

SUBSTITUTED ACID DERIVATIVES USEFUL AS ANTIDIABETIC AND  
ANTIOBESITY AGENTS AND METHOD

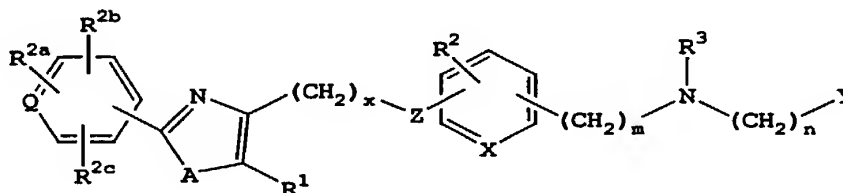
This is a continuation-in-part of U.S. application  
5 Serial No. 09/664,598, filed September 18, 2000 which  
application takes priority from U.S. provisional  
application No. 60/155,400 filed September 22, 1999.

## Field of the Invention

10       The present invention relates to novel substituted  
acid derivatives which modulate blood glucose levels,  
triglyceride levels, insulin levels and non-esterified  
fatty acid (NEFA) levels, and thus are particularly  
useful in the treatment of diabetes and obesity, and to a  
15   method for treating diabetes, especially Type 2 diabetes,  
as well as hyperglycemia, hyperinsulinemia,  
hyperlipidemia, obesity, atherosclerosis and related  
diseases employing such substituted acid derivatives  
alone or in combination with another antidiabetic agent  
20   and/or a hypolipidemic agent.

## Description of the Invention

In accordance with the present invention,  
substituted acid derivatives are provided which have the  
25 structure I  
I



wherein x is 1, 2, 3 or 4; m is 1 or 2; n is 1 or 2;

O is C or N;

A is 0 or S;

Z is 0 or a bond;

R<sup>1</sup> is H or alkyl;

X is CH or N;



R<sup>2a</sup>, R<sup>2b</sup> and R<sup>2c</sup> may be the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R<sup>3</sup> is H, alkyl, arylalkyl, aryloxy carbonyl, alkyloxy carbonyl, alkynyloxy carbonyl, alkenyloxy carbonyl, aryl carbonyl, alkyl carbonyl, aryl, heteroaryl, alkyl(halo)aryloxy carbonyl, alkyloxy(halo)aryloxy carbonyl, cycloalkylaryloxy carbonyl, cycloalkyloxyaryloxy carbonyl, cycloheteroalkyl, heteroaryl carbonyl, heteroaryl-heteroarylalkyl, alkyl carbonylamino, aryl carbonylamino, heteroaryl carbonylamino, alkoxycarbonylamino, aryloxy carbonylamino, heteroaryloxy carbonylamino, heteroaryl-heteroaryl carbonyl, alkylsulfonyl, alkenylsulfonyl, heteroaryloxy carbonyl, cycloheteroalkyloxy carbonyl, heteroarylalkyl, aminocarbonyl, substituted aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylalkenyl, cycloheteroalkyl-heteroarylalkyl; hydroxyalkyl, alkoxy, alkoxyaryloxy carbonyl, arylalkyloxy carbonyl, alkylaryloxy carbonyl, arylheteroarylalkyl, arylalkylarylalkyl, aryloxyarylalkyl, haloalkoxyaryloxy carbonyl, alkoxycarbonylaryloxy carbonyl, aryloxyaryloxy carbonyl, arylsulfinylaryl carbonyl, arylthioaryl carbonyl, alkoxycarbonylaryloxy carbonyl, arylalkenyloxy carbonyl, heteroaryloxyarylalkyl, aryloxyaryl carbonyl, aryloxyarylalkyloxy carbonyl, arylalkenyloxy carbonyl, arylalkyl carbonyl, aryloxyalkyloxy carbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, alkoxyarylalkyl, heteroarylalkoxy carbonyl, arylheteroarylalkyl, alkoxyaryl carbonyl, aryloxyheteroarylalkyl, heteroarylalkyloxyarylalkyl, arylarylalkyl, arylalkenylarylalkyl, arylalkoxyarylalkyl,

5 aminocarbonylarylalkyl;

10 structure  $P(O)(OR^{4a})_2$ , (where  $R^{4a}$  is H or a prodrug ester);

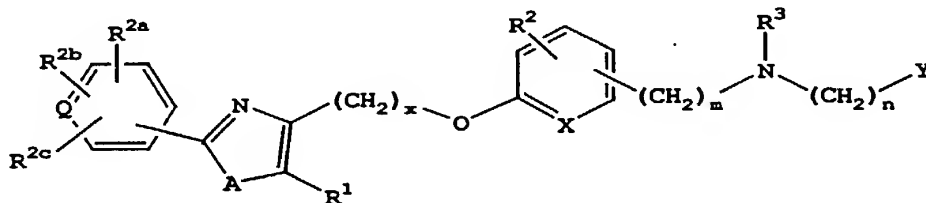
substituted with 1, 2 or 3 substituents;

15 thereof, with the proviso that

CO<sub>2</sub>R<sup>4</sup>, then R<sup>3</sup> is other than H or alkyl containing 1 to 5 carbons in the normal chain.

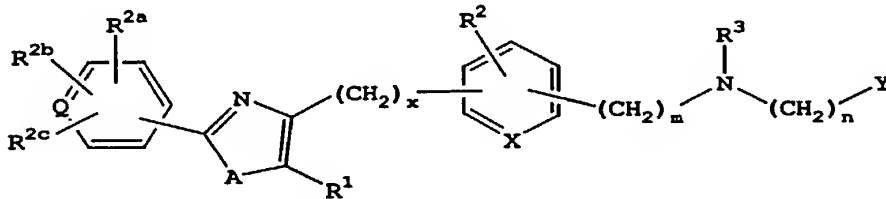
20 have the structure

Ia



or

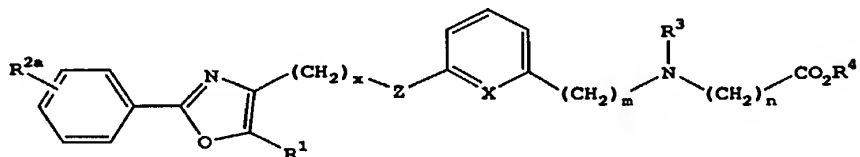
Ib



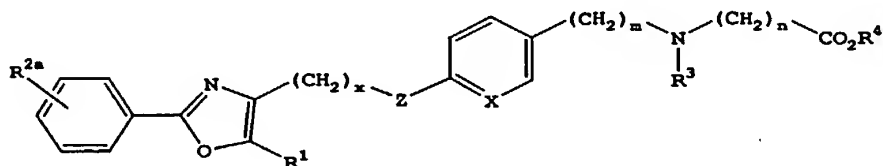
25

Preferred are compounds of formula I of the invention having the structure

5 IB



IC



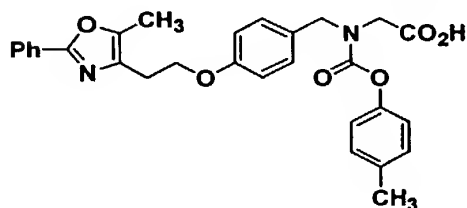
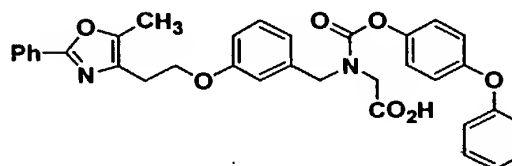
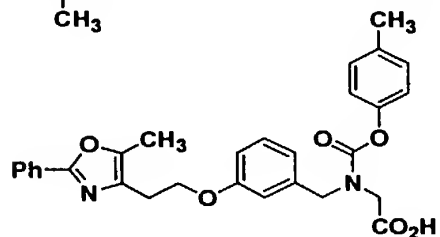
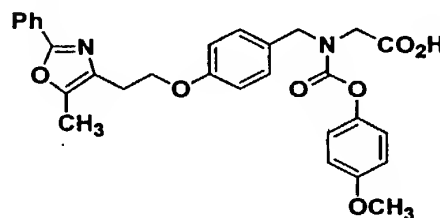
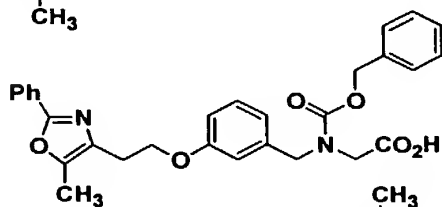
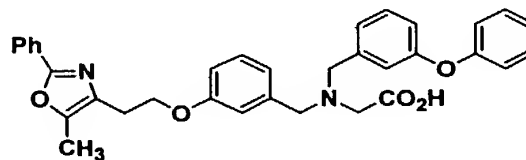
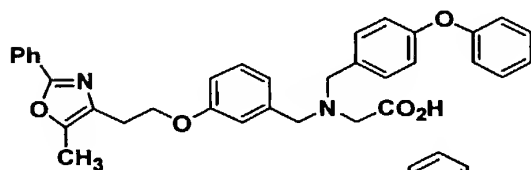
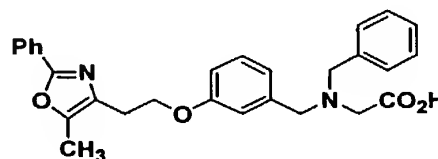
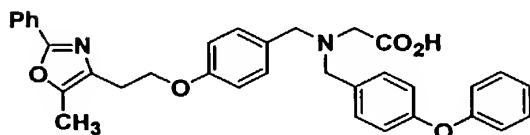
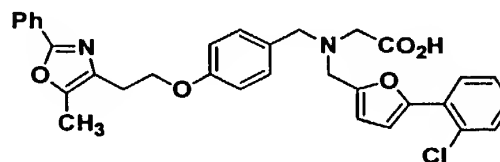
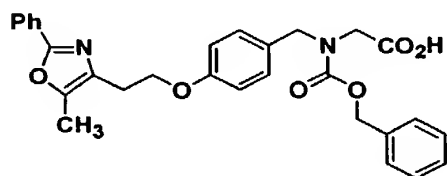
$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{---C---} \end{array}$ ,  $(\text{CH}_2)_m$  is  $\text{CH}_2$ , or  $\begin{array}{c} \text{R}_a \\ | \\ \text{---CH---} \end{array}$  (where  $\text{R}_a$  is alkyl such as methyl, or alkenyl such as  $\text{---CH}_2\text{---CH=CH}_2$  or  $\begin{array}{c} \text{---CH}_2\text{---C=CH}_2 \\ | \\ \text{CH}_3 \end{array}$ )  $(\text{CH}_2)_n$  is  $\text{CH}_2$ ,  $\text{R}^1$  is lower alkyl.

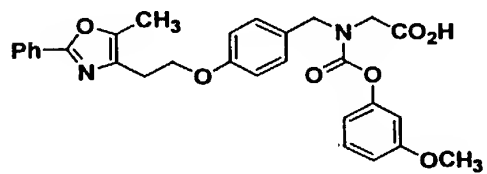
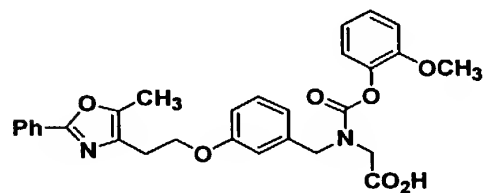
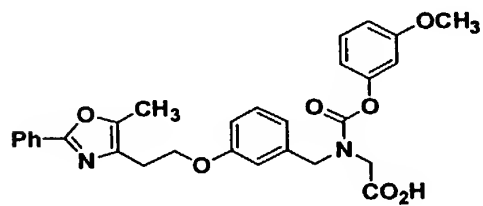
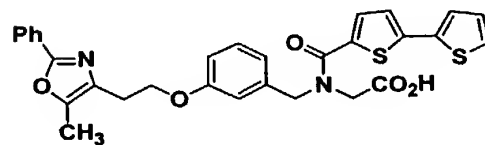
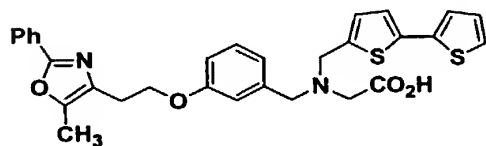
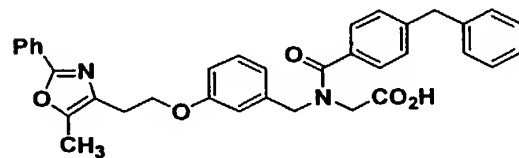
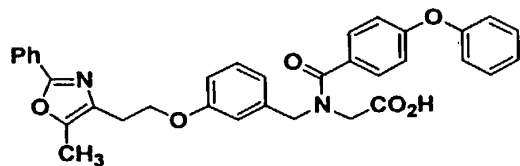
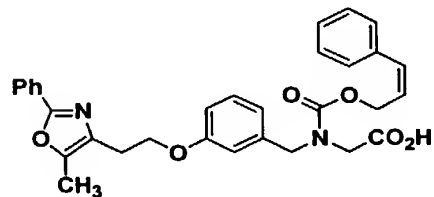
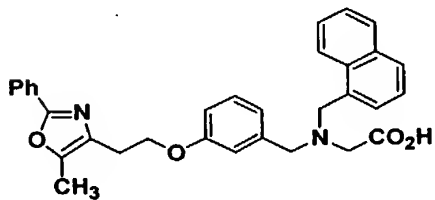
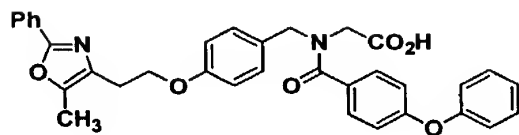
- 4 -

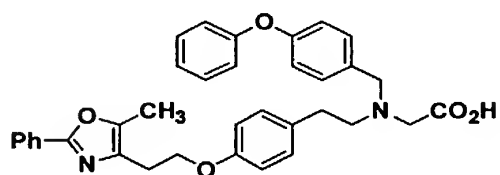
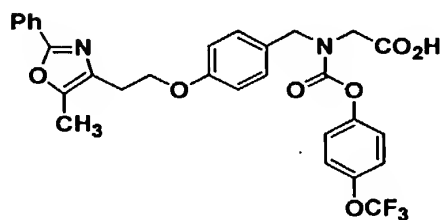
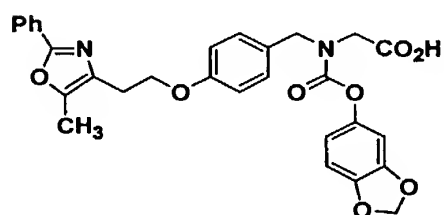
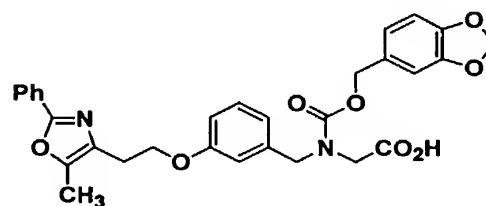
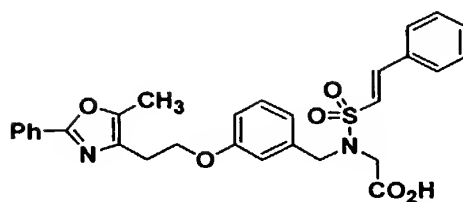


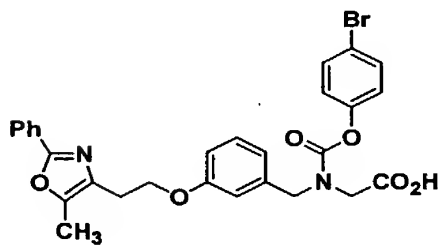
cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxy-carbonyl, wherein the above preferred groups may be optionally substituted.

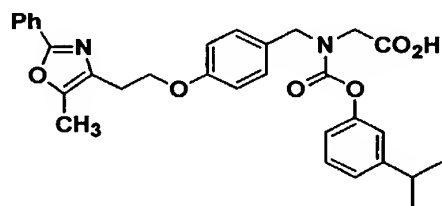
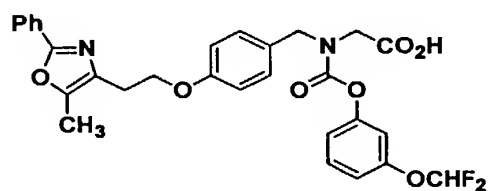
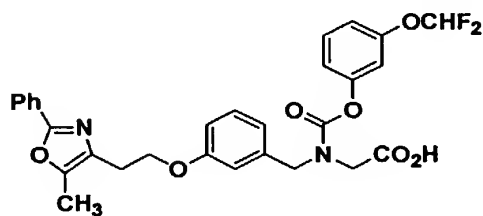
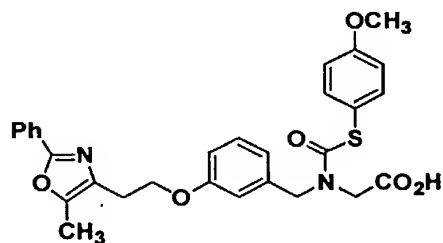
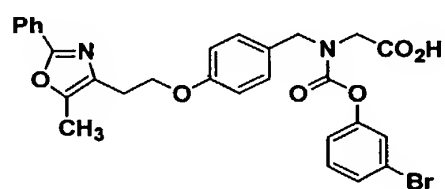
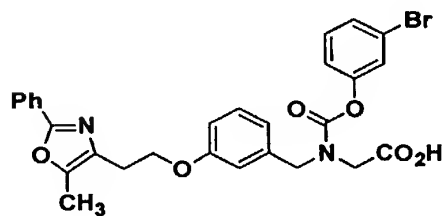
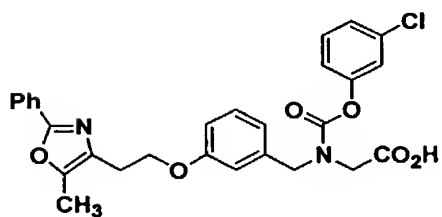
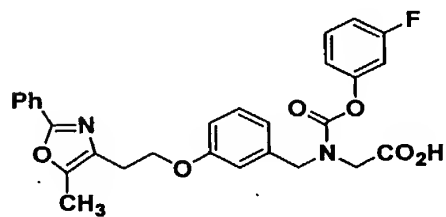
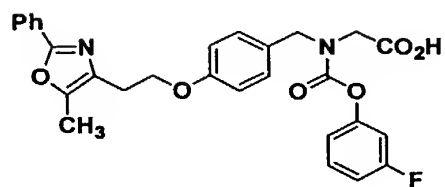
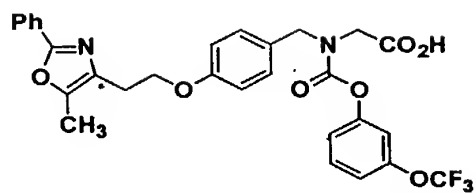
- 5 Preferred compounds of the invention include the following:





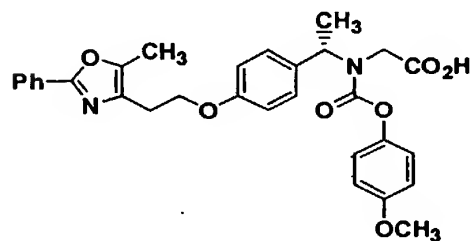
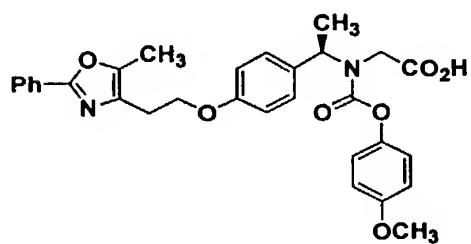
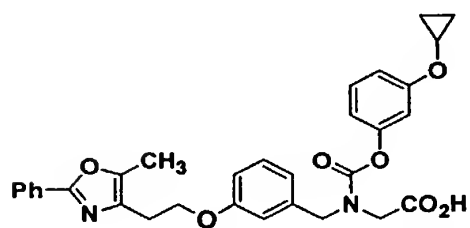
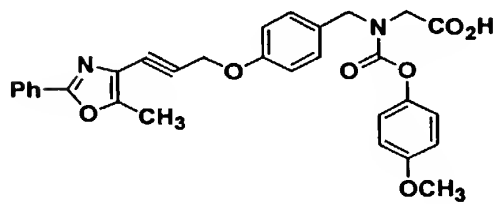
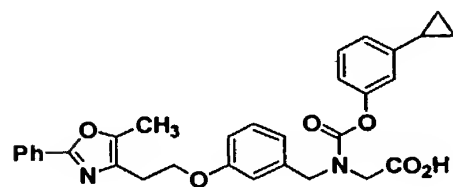
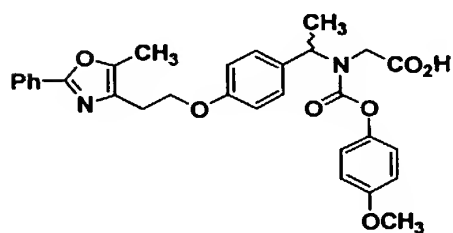
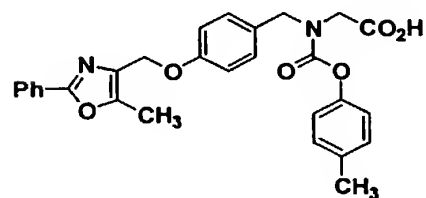
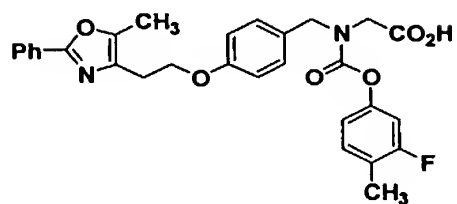
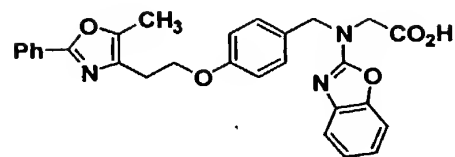
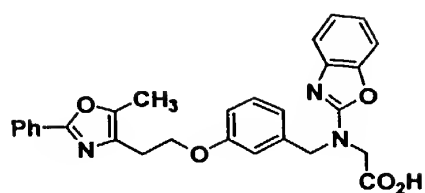




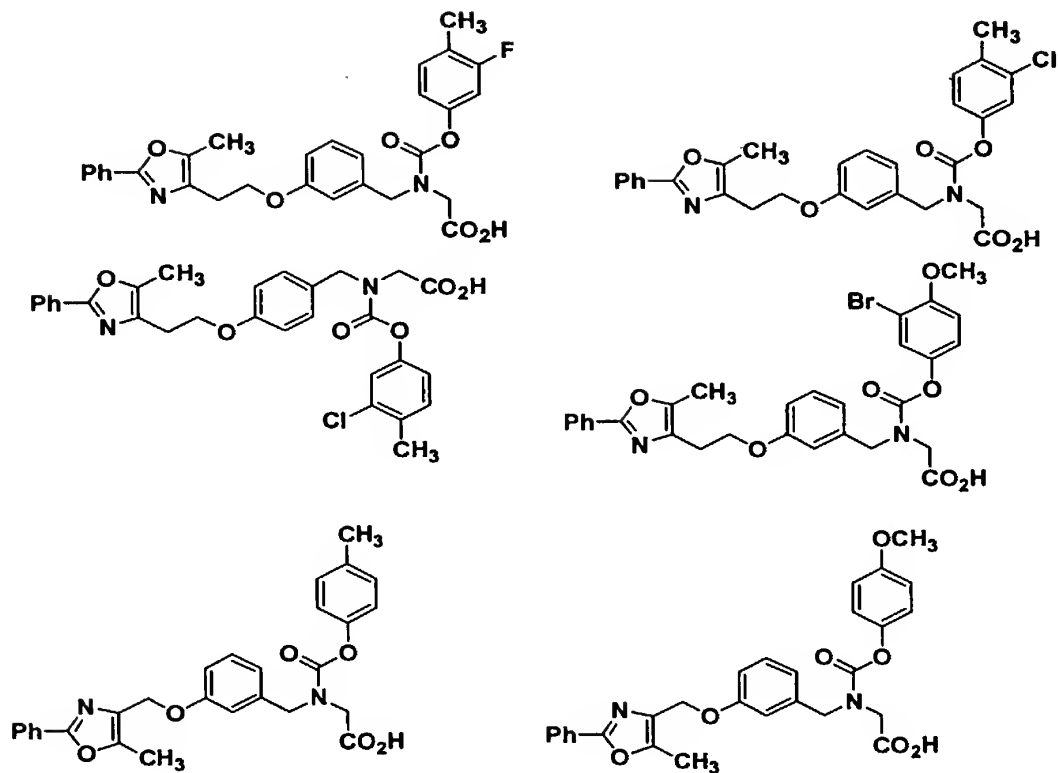
















10

dysmetabolic syndrome, atherosclerosis, and related diseases wherein a therapeutically effective amount of a compound of structure I is administered to a human patient in need of treatment.

5 In addition, in accordance with the present invention, a method is provided for treating early malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions (such as fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN),  
10 liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and osteoporosis and proliferative diseases  
15 such as psoriasis, wherein a therapeutically effective amount of a compound of structure I is administered to a human patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of structure I and another type antidiabetic agent and/or a hypolipidemic agent, and/or lipid modulating agent and/or other type of therapeutic agent, is administered to a human patient in need of treatment.

In the above methods of the invention, the compound of structure I will be employed in a weight ratio to the antidiabetic agent (depending upon its mode of operation) within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 10:1.

The conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Dysmetabolic Syndrome are detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 35 82, 727-734 (1997) and other publications.

The term "diabetes and related diseases" refers to Type II diabetes, Type I diabetes, impaired glucose

The conditions, diseases and maladies collectively referred to as "diabetic complications" include retinopathy, neuropathy and nephropathy, and other known complications of diabetes.

20           The term "lipid-modulating" agent as employed herein refers to agents which lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid disorders.

## Detailed Description of the Invention

30 general synthetic schemes, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these

reactions appear hereinafter and in the working Examples. Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M.,  
5 Protecting Groups in Organic Synthesis, 3<sup>rd</sup> Edition, 1999 [Wiley]).

Scheme 1 describes a general synthesis of the amino acids described in this invention. An alcohol II ( $R^5(CH_2)_xOH$ ) (of which the most favored is 2-phenyl-5-methyl-oxazole-4-ethanol) is coupled with a hydroxy aryl-  
10 or heteroaryl- aldehyde III (preferably 3- or 4-hydroxybenzaldehyde) under standard Mitsunobu reaction conditions (e.g. Mitsunobu, O., *Synthesis*, 1981, 1). The resulting aldehyde IV is then subjected to reductive  
15 amination using procedures known in the literature (e.g. Abdel-Magid et al, *J. Org. Chem.* 1996, 61, 3849) with an  $\alpha$ -amino ester hydrochloride V. PG in Scheme 1 denotes a preferred carboxylic acid protecting group, such as a methyl or tert-butyl ester. The resulting secondary  
20 amino-ester VI is then subjected to a second reductive amination using methods known in the literature (e.g. Abdel-Magid et al, *J. Org. Chem.* 1996, 61, 3849) with an  $R^{3a}$  aldehyde VII. Final deprotection of the carboxylic acid ester under standard conditions known in the  
25 literature (Greene) utilizing basic conditions (for methyl esters) or acidic conditions (for tert-butyl esters) then furnishes the desired amino acid products ID.

An alternative route to the aldehyde IV is shown in  
30 Scheme 1A. The alcohol II ( $R^5(CH_2)_xOH$ ) (of which the most favored is 2-[2-phenyl-5-methyl-oxazole-4-yl]-ethanol) is treated with methanesulfonyl chloride to give the corresponding mesylate VIII. The mesylate is then  
alkylated under standard basic conditions with a  
35 hydroxyaryl or hydroxyheteroaryl aldehyde III to furnish the aldehyde IV.

An alternative route to the amino acids IF is shown in Scheme 2. The secondary amino-ester VI is deprotected under standard conditions (basic conditions if the protecting group (PG) is methyl; acidic conditions if PG is tert-butyl) to furnish the corresponding amino acid IE. Reductive amination with an  $R^{3a}$  aldehyde under analogous conditions as described in Scheme 1 furnishes the desired tertiary amino acid products IF.

Alternatively, as shown in Scheme 3, the tertiary amino acids IF may also be obtained by alkylation of the secondary amino-ester VI with an alkylating agent IX (with an appropriate leaving group (LG) such as halide, mesylate, or tosylate) under standard conditions known in the art followed again by standard deprotection of the carboxylic acid ester X to provide the amino acids IF.

As shown in Scheme 4, the tertiary amino acid IF may also be assembled through reductive amination first of the  $R^{3a}$  aldehyde XI with an appropriate amine ester hydrochloride V. The resulting secondary amine-ester XII then is subjected to reductive amination with the appropriate alkyl, aryl or heteroaryl aldehyde IV (as in Scheme 1) followed by deprotection of the carboxylic acid ester to give the desired amino acid analogs IF.

For further substituted amino acids, a general synthetic scheme is shown in Scheme 5. Reductive amination of an appropriate amine XIII with an aryl or heteroaryl aldehyde XIV under standard conditions furnishes the corresponding secondary amine XV, which is then reacted with a halide-ester XVI (e.g. tert-butyl bromoacetate) to furnish the corresponding  $\alpha$ -amino ester XVII. This amine-ester XVII is then deprotected under standard conditions to provide the desired amino acid analogs IF.

The synthetic route in Scheme 5 also provides a general scheme for the synthesis of the corresponding aminophosphonic acids IFA, as illustrated in Scheme 5a. The secondary amine XV is reacted with an appropriately

An alternative to the sequence in Scheme 5 is shown in Scheme 6. A hydroxyaryl or heteroaryl amine XVIII is selectively protected on nitrogen to provide protected amine XIX. A preferred  $R^5(CH_2)_nOH$  (II) is then reacted with XIX under Mitsunobu conditions to provide the corresponding ether, followed by deprotection of the amine, to form the free amine XX. The free amine XX is then activated with a standard activating group (2,4-dinitrobenzenesulfonamide; T. Fukuyama et al, *Tetrahedron Lett.* **1997**, 38, 5831) and is then treated with an  $\alpha$ -halo ester XVI as in Scheme 5. The 2,4 dinitrobenzenesulfonamide XXI is deprotected under literature conditions (T. Fukuyama et al, *Tetrahedron Lett.*, **1997**, 38, 5831) to furnish a secondary  $\alpha$ -amino-ester XXII which is then subjected to a reductive amination with an  $R^{3a}$  aldehyde XI followed by deprotection of the ester X to furnish the desired analogs IF.

- 20 -



Scheme 8 describes a general synthesis of diaryl and aryl-heteroaryl-substituted amino acid analogs IH.

10 coupling (e.g. conditions as described in Gibson, S. E.,  
Transition Metals in Organic Synthesis, A Practical  
Approach, pp. 47-50, 1997) with aryl or heteroaryl  
halides XXVIII (especially bromides) to furnish the  
appropriate cross-coupling diaryl products XXIX.  
15 Deprotection of the amine-ester XXIX generates the  
desired amino acid analogs IH.

described in Scheme 8 can be coupled with appropriately substituted phenols XXX under literature conditions (D. A. Evans et al, *Tetrahedron Lett.*, **1998**, 39, 2937) to furnish the appropriate diaryl or aryl-heteroaryl ethers XXXI, which after deprotection afford the desired amino acid analogs IJ.

30 corresponding phenol-tertiary amine-ester XXXIII. The phenol XXXIII can then undergo coupling with appropriate aryl or heteroaryl boronic acids XXXIV under literature conditions (D. A. Evans et al, *Tetrahedron Lett.*, **1998**, 39, 2937) to furnish the corresponding diaryl or  
35 arylheteroaryl ether-amino esters XXXI. The desired analogs IJ are then obtained after deprotection of the amine-ester XXXI.

Scheme 11 illustrates the synthesis of the carbamate-acid analogs IK. The secondary amine-ester XXII can be reacted with appropriate chloroformates XXXV under standard literature conditions (optimally in  $\text{CH}_2\text{Cl}_2$  or  $\text{CHCl}_3$  in the presence of a base such as  $\text{Et}_3\text{N}$ ) to furnish the corresponding carbamate-esters. The requisite analogs IK are then obtained after deprotection of the carbamate-ester. Alternatively, the secondary amine-ester XXII can be reacted with phosgene to generate the corresponding carbamyl chloride XXXVI. This carbamyl chloride intermediate XXXVI can be reacted with  $\text{R}^{3a}\text{-OH}$  (XXXVII) (optimally substituted phenols) to afford the corresponding carbamate-acids IK after deprotection.

Scheme 12 illustrates the further functionalization of aryl carbamate-acid analogs IK. The secondary amine-ester XXII is reacted with an aryl chloroformate XXXVIII (containing a protected hydroxyl group) to form XXXIX. The hydroxyl group is then selectively deprotected in the presence of the ester functionality to provide XL, then alkylated with an appropriate  $\text{R}^6\text{-LG}$  (XLI) (where LG is halide, mesylate or tosylate, and  $\text{R}^6$  is most preferably  $\text{CHF}_2\text{-}$ , or  $\text{CH}_3\text{CH}_2\text{-}$ ) in the presence of base. Deprotection of the ester then furnishes the desired carbamate-acid analogs IL.

The secondary amine-ester XXIIA can be functionalized with substituted aryl or aliphatic carboxylic acids XLII, under standard peptide coupling conditions, as illustrated in Scheme 13. The amide bond-forming reactions are conducted under standard peptide coupling procedures known in the art. Optimally, the reaction is conducted in a solvent such as DMF at  $0^\circ\text{C}$  to RT using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDAC or EDCI or WSC), 1-hydroxybenzotriazole (HOBT) or 1-hydroxy-7-azabenzotriazole (HOAT) and a base, for example Hunig's base (diisopropylethylamine), N-methylmorpholine or triethylamine. Deprotection of the amide-ester then furnishes the desired amide-acid analogs IM.

The secondary amine-ester XXIIA can also be reacted with aliphatic or aryl isocyanates XLIII to provide the corresponding urea-esters. Deprotection of the urea-ester provides the desired urea-acid analogs IN, as shown in Scheme 14. Alternatively, as shown in Scheme 15, the carbamyl chloride intermediate XXXVI described in Scheme 11 can be reacted with appropriate aliphatic or aryl amines XLIV in the presence of a tertiary amine (e.g. Et<sub>3</sub>N) to furnish tri- or tetrasubstituted urea-acid analogs IO or IP after deprotection of the ester.

The secondary amine-ester XXIIA can also be reacted with appropriate sulfonyl chlorides XLVI under standard literature conditions (optimally in the presence of a base such as pyridine, either neat or using chloroform as a co-solvent), followed by deprotection, to provide the corresponding sulfonamide-acids IQ, as shown in Scheme 16.

Replacement of the carboxylic acid functionality in these analogs with tetrazole can be achieved as shown in Scheme 17. An acid analog IK is coupled with an amine (containing an appropriate tetrazole protecting group) XLVII (preferably 3-amino propionitrile) under standard peptide coupling conditions. The resulting secondary amide XLVIII is then subjected to a Mitsunobu reaction under standard conditions with trimethylsilyl azide (TMSN<sub>3</sub>) to form the protected tetrazole XLIX. Deprotection of the cyanoethyl group is achieved preferentially in the presence of base to generate the desired free tetrazole analog IR.


Scheme 18 describes a general synthesis of the hydrazide-acid analogs IS. A substituted aryl carboxylic acid 1 is treated with methanesulfonyl chloride in the presence of base; the intermediate is then reacted with a protected hydrazine-ester VA to give the corresponding acylated hydrazine 1a (ref: *Synthesis*, 1989, 745-747). The acylhydrazine 1a is coupled with an appropriately substituted aryl aldehyde IV under reductive amination

conditions to give the corresponding protected hydrazide ester 3 (ref: Can. J. Chem., 1998, 76, 1180-1187).

Deprotection of the ester 3 then furnishes the hydrazide-acid analogs IS.

5           An alternative synthetic approach to hydrazide-acids IS is shown in Scheme 19. An aryl aldehyde IV can be reduced to the corresponding alcohol under standard conditions (e.g.  $\text{NaBH}_4$ ). This alcohol is then converted to the corresponding bromide 4 using standard conditions  
10       (e.g.  $\text{Ph}_3\text{P/CBr}_4$  or  $\text{PBr}_3$ ). The bromide 4 is then reacted with the hydrazine-ester 1a (ref: *Tetrahedron Lett.*, 1993, 34, 207-210) to furnish the protected hydrazide-ester 3, which is then deprotected to give the hydrazide-acid analogs IS.

15           The different approaches to the preparation of the  $\alpha$ -alkylbenzyl amino acid and carbamate-acid analogs IT and IU are exemplified in the following synthetic schemes. In Scheme 20 an appropriately substituted aryl aldehyde IV is treated with a suitable organometallic  
20       reagent (e.g. a Grignard reagent  $\text{R}^{10}\text{MgBr}$ ) under standard conditions to give the corresponding secondary alcohol, which is then oxidized under standard conditions (e.g. Swern oxidation with  $(\text{COCl})_2/\text{DMSO}/\text{Et}_3\text{N}$  or using pyridinium chlorochromate) to give the corresponding ketone 5.  
25       Reductive amination of the ketone 5 with an appropriately substituted amino-ester 6 provides the corresponding  $\alpha$ -alkylbenzyl amino-ester 7. It will be understood that in

the amino ester 6, the moiety  does not necessarily represent two repeating units.

30           Acylation of amino-ester 7 with an appropriately substituted aryl or heteroaryl chloroformate XXXV followed by deprotection provides the racemic carbamate-acid analogs IT. Reductive amination of alkylbenzyl amino-ester 7 with aryl aldehyde VII followed by  
35       deprotection provides the racemic amino-acid analogs IU.

Alternatively, as shown in Scheme 21, asymmetric reduction (e.g. using the Corey oxazaborolidine reduction protocol; review: E. J. Corey & C. Helal, *Angew. Chem. Int. Ed. Engl.*, 1998, 37, 1986-2012.) of the aryl-ketone 5 provides each of the desired enantiomeric alcohols 8 (although only one enantiomer is represented in the scheme). Treatment of the chiral alcohol 8 with azide in a Mitsunobu-like reaction (ref: A. S. Thompson et. al., *J. Org. Chem.* 1993, 58, 5886-5888) gives the corresponding chiral azide (with inverted stereochemistry from the starting alcohol). The azide is then converted to the amine 9 by standard reduction methods (e.g. hydrogenation or  $\text{Ph}_3\text{P}/\text{THF}/\text{H}_2\text{O}$ ). Treatment of the chiral amine 9 with an ester XVIA (containing an appropriate leaving group) provides the secondary amino-ester 10. Acylation of amino-ester 10 with an aryl or heteroaryl chloroformate XXXV followed by deprotection provides the chiral carbamate-acid analogs ITa (which may be either enantiomer depending upon the stereochemistry of 8). Reductive amination of alkyl amino-ester 10 with aryl aldehydes VII followed by deprotection provides the chiral amino-acid analogs IUa (which may be either enantiomer depending upon the stereochemistry of 8).

An alternative to Scheme 21 is shown in Scheme 22. An appropriately protected oxyaryl ketone 11 undergoes asymmetric reduction to give the chiral alcohol 12. This is converted to the chiral amine 13 via the identical sequence as in Scheme 21 (via the chiral azide). Treatment of the chiral amine 13 with an ester XVIA (LG = halogen or mesylate) gives the corresponding secondary amino-ester 14. Acylation of 14 with an aryl or heteroaryl chloroformate XXXV provides the corresponding carbamate-ester. Selective deprotection furnishes the free phenol carbamate-ester 15. Alkylation of the phenol 15 with a halide or mesylate VIII followed by deprotection provides the carbamate-acid analogs ITa. An analogous sequence (involving reductive amination of the

secondary amino-ester 14 with an aryl or heteroaryl aldehyde VII, then selective deprotection, alkylation with VIII and a final deprotection) provides the amino acid analogs IUa.

5           It will be appreciated that either the (R)- or (S)-  
enantiomer of ITa or IUa may be synthesized in Schemes 21  
and 22, depending upon the chirality of the reducing  
agent employed.

A fourth synthetic sequence is shown in Scheme 23. The substituted aldehyde IV is condensed with an amino-ester hydrochloride 6 to give the corresponding imine 16, which is then treated in situ with an appropriately substituted allylic halide 17 in the presence of indium metal (reference: Loh, T.-P., et al., *Tetrahedron Lett.*, 1997, 38, 865-868) to give the  $\alpha$ -allyl benzyl amino-ester 18. Acylation of amine 18 with an aryl or heteroaryl chloroformate XXXV followed by deprotection provides the carbamate-acid analogs IV. Reductive amination of alkyl amino-ester 18 with an aryl or heteroaryl aldehyde VII followed by deprotection provides the amino-acid analogs IW.

Scheme 24 shows the preparation of the required intermediate 2-aryl-5-methyl-oxazol-4-yl methyl chloride 21 (following the general procedure described in Malamas, M. S., et al, *J. Med. Chem.*, 1996, 39, 237-245). A substituted aryl aldehyde 19 is condensed with butane-2,3-dione mono-oxime under acidic conditions to give the corresponding oxazole N-oxide 20. Deoxygenation of the oxazole N-oxide 20 with concomitant chlorination furnishes the desired chloromethyl aryl-oxazoles 21. Hydrolysis of chloromethyl oxazole 21 under basic conditions furnishes the corresponding oxazole-methanol 22. Oxidation of alcohol 22 to the corresponding aldehyde is followed by conversion to the corresponding dibromoalkene 23 (e.g.  $\text{Ph}_3\text{P/CBr}_4$ ). The dibromide 23 is converted to the corresponding alkynyl-lithium species (using an organolithium reagent such as *n*-BuLi), which

can be reacted in situ with an appropriate electrophile such as formaldehyde to give the corresponding acetylenic alcohol (ref: Corey, E. J., et al., *Tetrahedron Lett.* 1972, 3769, or Gangakhedkar, K. K., *Synth. Commun.* 1996, 26, 1887-1896). This alcohol can then be converted to the corresponding mesylate 24 and alkylated with an appropriate phenol 25 to provide analogs IX. Further stereoselective reduction (e.g. H<sub>2</sub>/Lindlar's catalyst) provides the E- or Z- alkenyl analogs IY.

10 Scheme 25 describes a general synthesis of the amino-benzoxazole analogs IZ (general ref: Sato, Y., et al, *J. Med. Chem.* 1998, 41, 3015-3021). An appropriately substituted ortho-aminophenol 26 is treated with CS<sub>2</sub> in the presence of base to furnish the corresponding  
15 mercapto-benzoxazole 27. Treatment of this thiol 27 with an appropriate chlorinating agent (e.g. PCl<sub>5</sub>) provides the key intermediate chlorobenzoxazole 28, which is reacted with the secondary amino-ester VI to furnish, after deprotection, the amino benzoxazole-acid analogs IZ.

20 The thiazole analogs IZa were synthesized according to the general synthetic route outlined in Scheme 26 (ref. Collins, J. L., et al., *J. Med. Chem.* 1998, 41, 5037). The secondary amino-ester XXIII is reacted with an aryl or heteroaryl chloroformate XXXV in the presence  
25 of an appropriate base (e.g. pyridine or triethylamine) to furnish the corresponding hydroxyaryl carbamate-ester 29. The hydroxyaryl ester 29 is then reacted with an appropriately substituted  $\alpha$ -bromo vinyl ketone 29a (for S<sub>3</sub> = CH<sub>3</sub>, e.g. Weyerstahl, P., et. al., *Flavour Fragr. J.*,  
30 1998, 13, 177 or Sokolov, N. A., et al., *Zh. Org. Khim.*, 1980, 16, 281-283) in the presence of an appropriate base (e.g. K<sub>2</sub>CO<sub>3</sub>) to give the corresponding Michael reaction adduct, the  $\alpha$ -bromoketone carbamate-ester 30. The  $\alpha$ -bromoketone 30 is then subjected to a condensation  
35 reaction with an appropriately substituted aryl amide 31 (A = O) or aryl thioamide 31 (A = S) to furnish either the corresponding oxazole (from the amide) or the

thiazole (from the thioamide) (ref: Malamas, M. S., et al, *J. Med. Chem.*, 1996, 39, 237-245). Finally, deprotection of esters 31 then provides the substituted oxazole and thiazole carbamate acid analogs IZa.

5 It will be appreciated that in the following  
schemes where the carbamate-acid analogs are prepared,  
the corresponding amino acid analogs may also be prepared  
by replacing the chloroformate reaction with an aldehyde  
in a reductive amination reaction (as in Scheme 20 with  
10 intermediate amine 7).

Scheme 27 describes a general synthesis of the acids IZb and IZc. A halo-substituted aryl aldehyde 32 (preferably iodide or bromide) is subjected to reductive amination using procedures known in the literature (e.g. Abdel-Magid et al, *J. Org. Chem.* 1996, 61, 3849) with an  $\alpha$ -amino acid ester hydrochloride V. The resulting secondary amino-ester 33 is then reacted with an aryl or heteroaryl chloroformate XXXV in the presence of an appropriate base (e.g. pyridine or triethylamine) to furnish the corresponding halo-aryl carbamate-ester 34. Aryl halide 34 is then reacted with an appropriate aryl- or heteroaryl-substituted acetylene 35 (the preferred acetylene being 5-phenyl-2-methyl-oxazol-4-yl-methylacetylene) in the presence of an appropriate palladium catalyst (e.g.  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ ) and a copper (I) salt (e.g. CuI) in a Sonogashira coupling reaction (ref: *Organocopper Reagents, a Practical Approach*, R. J. K. Taylor, Ed., Chapter 10, pp 217-236, Campbell, I. B., Oxford University Press, 1994) to furnish the key intermediate, arylacetylene carbamate ester 36.

The arylacetylene ester 36 is deprotected to provide the corresponding arylacetylene acid analogs 1Zb. The acetylene moiety of 36 can be reduced by standard methods (e.g. hydrogenation, ref: M. Hudlicky, 35 Reductions in Organic Chemistry, 2<sup>nd</sup> Edition, ACS, 1996, Chapter 1) to furnish the corresponding fully saturated



alkyl aryl carbamate ester, which is then deprotected to give the alkyl aryl carbamate acid analogs IZc.

Stereoselective reduction of the acetylene ester 36 by standard methods (e.g. Lindlar's catalyst; ref: 5 Preparation of Alkenes, A Practical Approach, J. J. Williams, Ed., Chapter 6, pp 117-136, Oxford University Press, 1996) can be achieved to provide the corresponding cis-alkenyl aryl carbamate-ester, which is then deprotected to furnish the Z-alkenyl aryl carbamate acid 10 analogs IZd (Scheme 28). Alternatively, this sequence can be reversed, i.e. the initial step being the deprotection of acetylenic ester 36 to the acetylenic acid, followed by stereoselective reduction of the acetylene moiety to provide the Z-alkene-acid analogs 15 IZd.

The corresponding trans-alkenyl aryl carbamate acids IZe can be synthesized according to the general route in Scheme 29. An aryl- or heteroaryl-acetylene 35 (the preferred moiety again being 5-phenyl-2-methyl-oxazol-4-yl-methylacetylene) is halogenated under 20 standard conditions (ref: Boden, C. D. J. et al., *J. Chem. Soc. Perkin Trans. I*, 1996, 2417; or Lu, W. et al., *Tetrahedron Lett.* 1998, 39, 9521) to give the corresponding halo-acetylene, which is then converted to 25 the corresponding trans-alkenyl stannane 37 (ref: Boden, C. D. J., *J. Chem. Soc., Perkin Trans. I*, 1996, 2417). This aryl- or heteroaryl-substituted trans-alkenyl stannane 37 is then coupled with the halo-aryl carbamate ester 34 under standard Stille coupling conditions (ref: 30 Farina, V. et. al., "The Stille Reaction", *Organic Reactions*, 1997, 50, 1) to furnish the corresponding trans-alkenyl aryl carbamate ester 38. This carbamate-ester is then deprotected under standard conditions to give the desired trans-alkenyl aryl carbamate acid 35 analogs IZe.

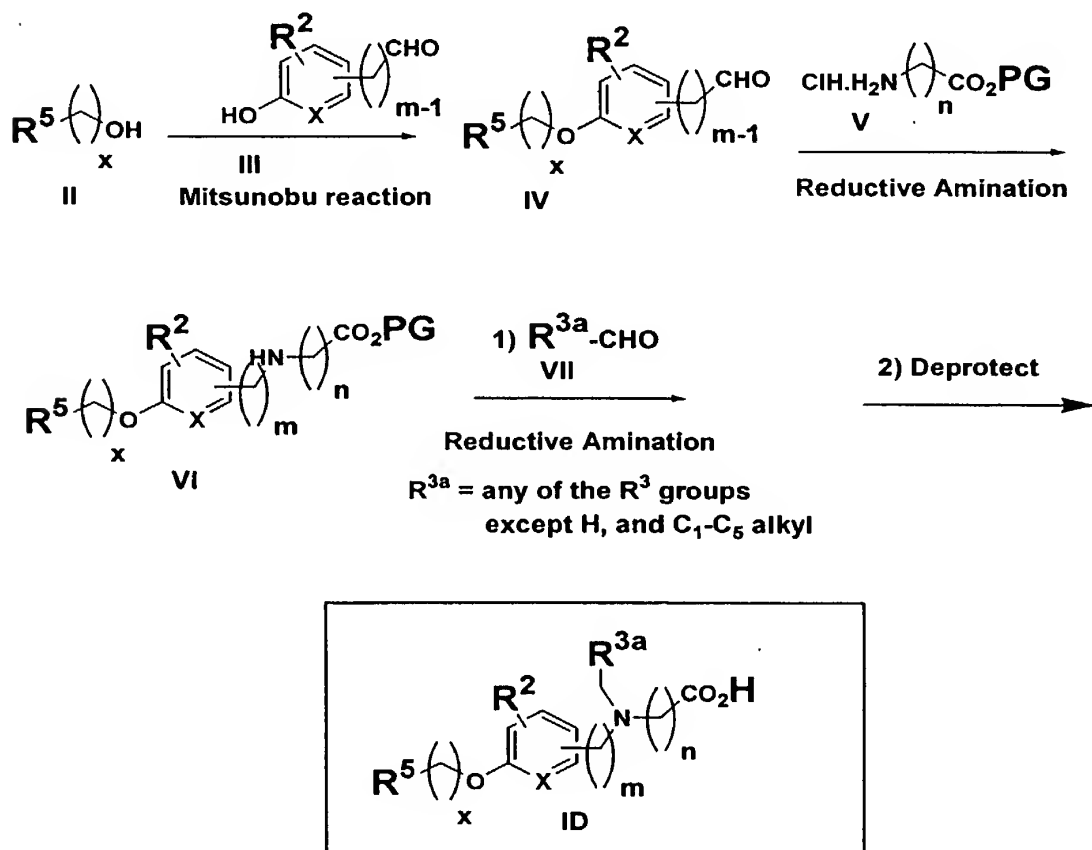
The corresponding cyclopropyl analogs IZf and IZg are synthesized according to Scheme 30. For the cis- or

(Z-) cyclopropyl analogs, stereoselective reduction ( $H_2$ /Lindlar's catalyst) of the alkynyl moiety of intermediate alkynyl ester 36 (as for analogs IZd), followed by cyclopropanation under standard conditions (Zhao, Y., et al, *J. Org. Chem.* 1995, 60, 5236-5242) and finally deprotection provides the cis-cyclopropyl carbamate-acid analogs IZf. For the trans-cyclopropyl analogs IF, analogous cyclopropanation of the E-alkene moiety of intermediate 38 followed by deprotection provides the trans-cyclopropyl carbamate-acid analogs IZg.

A preferred alternative asymmetric synthesis of ITa (Scheme 21) is shown in Scheme 31. Protection of a chiral amine 39 (with the phenol protected), preferably as a carbamate, provides intermediate 40. Removal of the phenolic protecting group of 40 provides the free phenol 41. Alkylation of phenol 41 with the mesylate VIII furnishes the protected amine 42. Deprotection of this amine then furnishes the key intermediate secondary amino-ester 9, which is then carried on to analogs ITa and IUa according to Scheme 21.

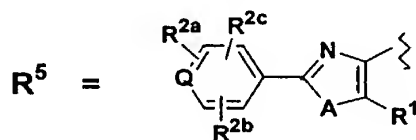
A preferred asymmetric synthesis of analogs IIA is shown in Scheme 32. The aldehyde IV is subjected to standard Wittig reaction conditions (ref: Preparation of Alkenes, a Practical Approach, J. J. Williams, Ed., Chapter 2, pp 19-58) to furnish the alkene 43. Asymmetric aminohydroxylation according to known literature procedures (ref: O'Brien, P., *Angew. Chem. Int. Ed.*, 1999, 38, 326 and Reddy, K. L., and Sharpless, K. B., *J. Am. Chem. Soc.*, 1998, 120, 1207) furnishes the desired amino-alcohol 44 as a single enantiomer. Selective protection of the amine provides the alcohol 45. Alcohol 45 is then converted to the intermediate 46, which contains a suitable leaving group (either a halide or a mesylate) for the subsequent cuprate reaction. Reaction of an appropriate higher-order cuprate (ref: L. A. Paquette, Ed., *Organic Reactions*, 1992, Vol. 41, J. Wiley & Sons) with the protected amine substrate 46

provides the coupled protected amine 47. Deprotection of the amine functionality of 47, followed by reaction with an ester XVIA (LG = halogen or mesylate), furnishes the corresponding secondary amino-ester 48. Acylation of 48 with an aryl or heteroaryl chloroformate XXXV provides the corresponding carbamate-ester, which is then deprotected to furnish the carbamate-acid analogs IIA.

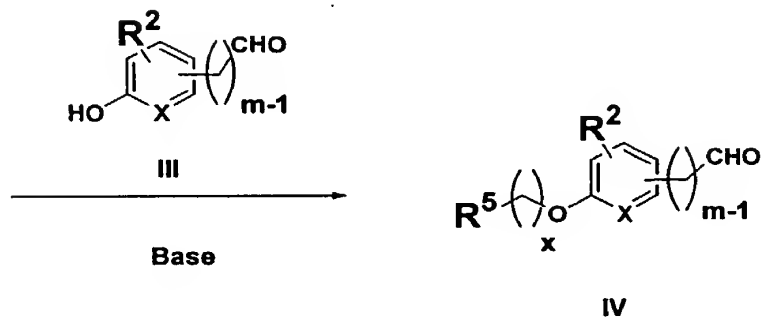
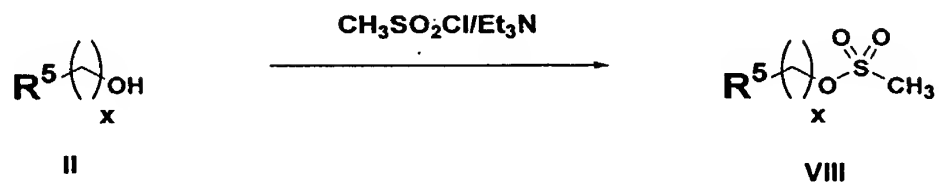


### Scheme 1

**In this and the following Reaction Schemes:**

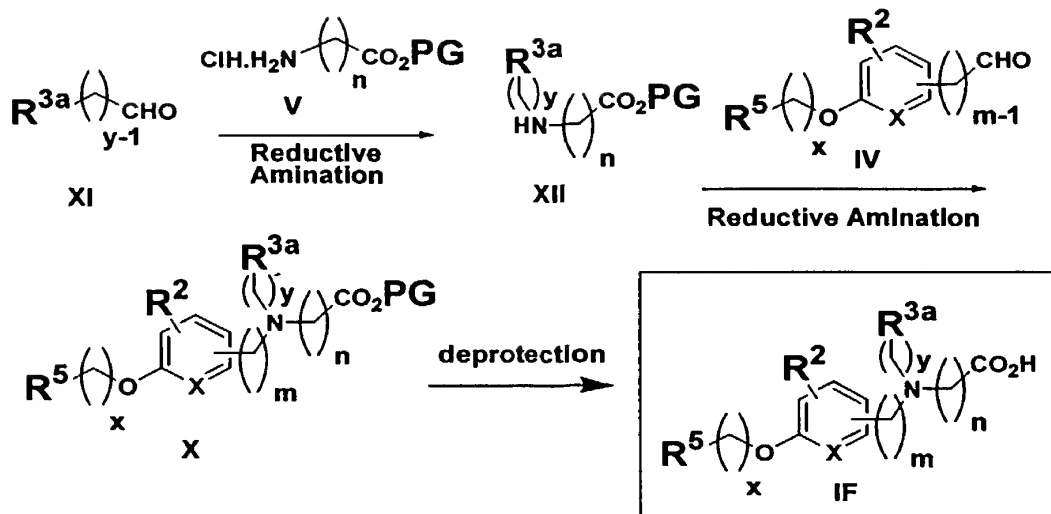


### Alternative Scheme 1A for Preparing Aldehyde IV

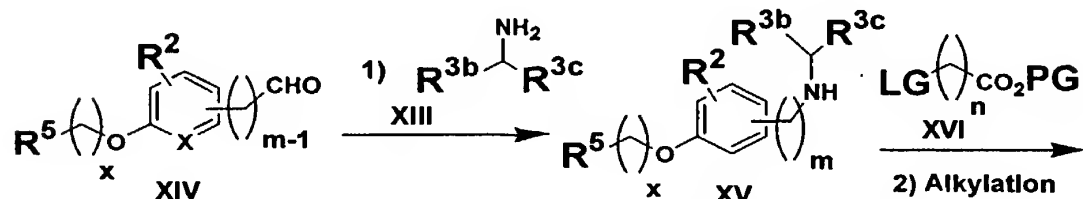


**SCHEME 1A**

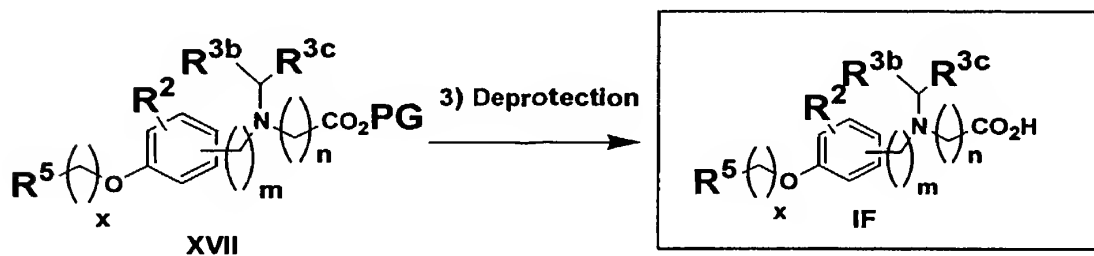




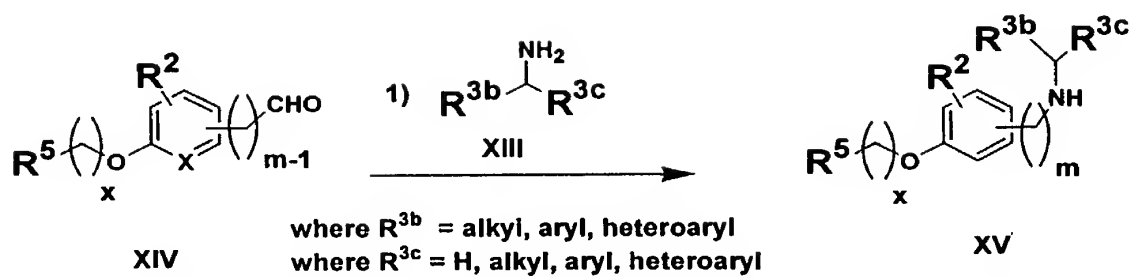
Scheme 4



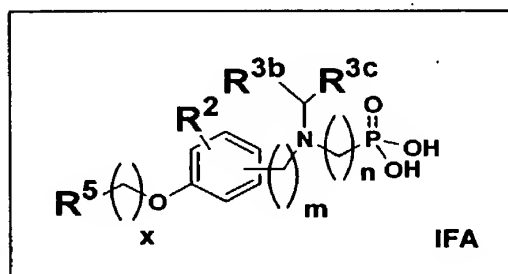
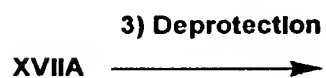
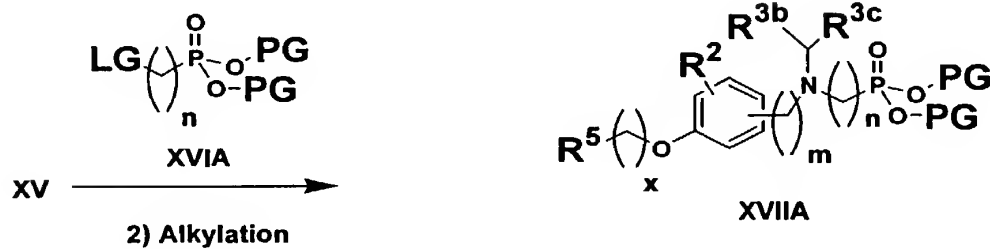
where  $\text{R}^{3b}$  = alkyl, aryl or heteroaryl  
 where  $\text{R}^{3c}$  = H, alkyl, aryl or heteroaryl  
 reductive amination



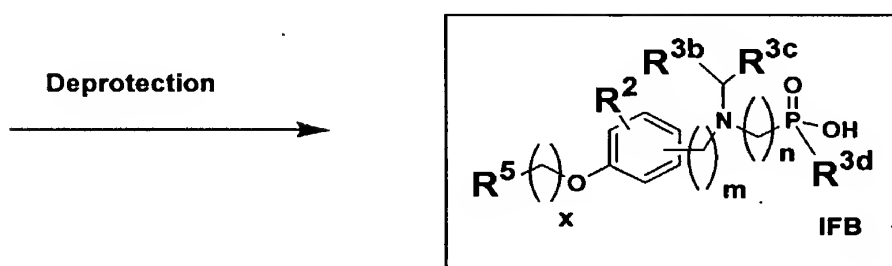
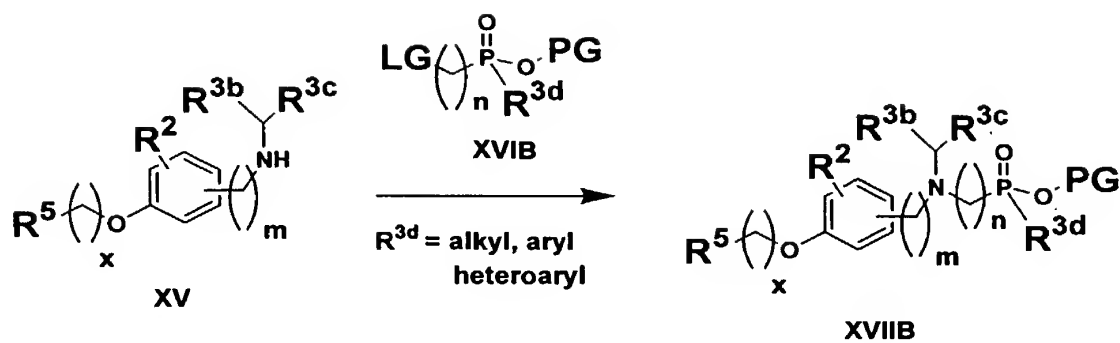
Scheme 5



reductive amination

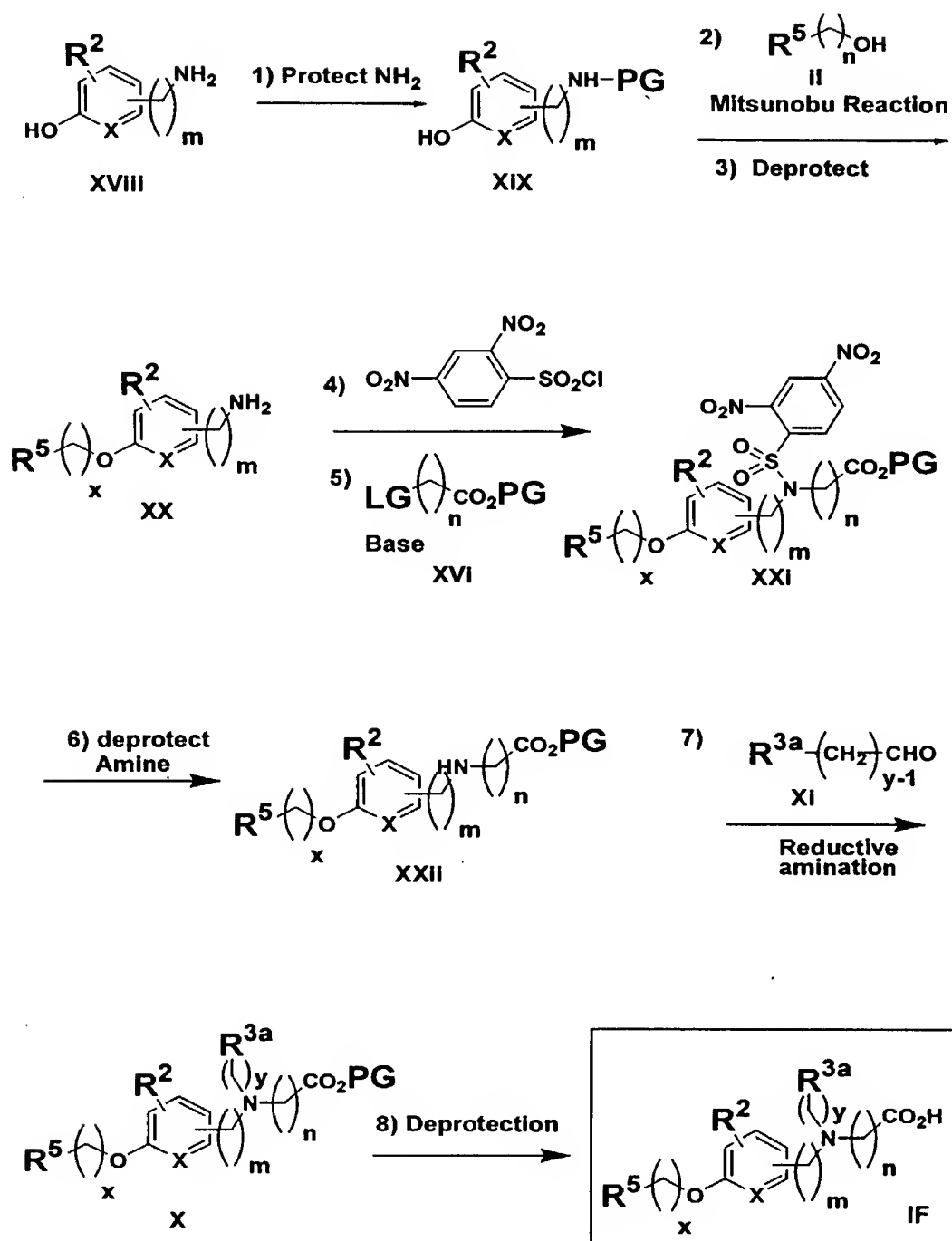


Scheme 5a



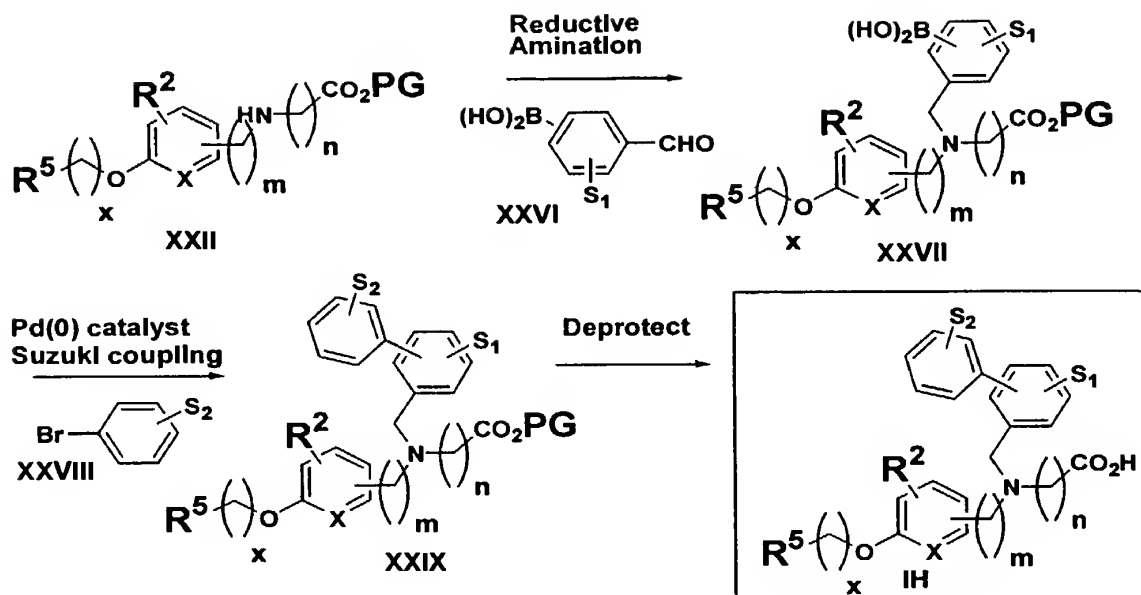
Scheme 5b





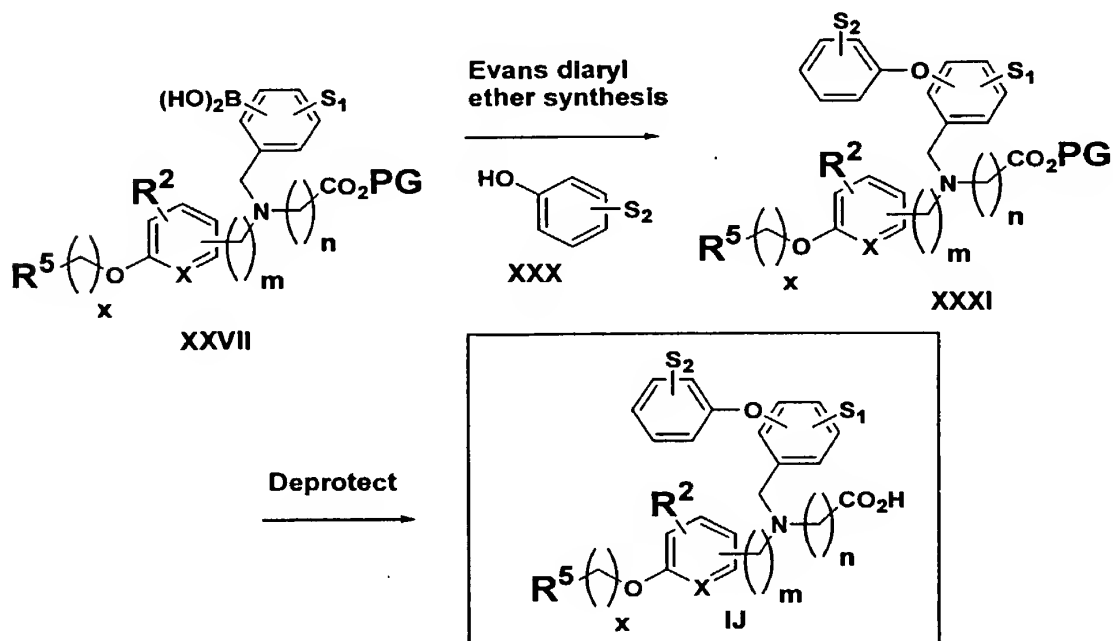
Scheme 6



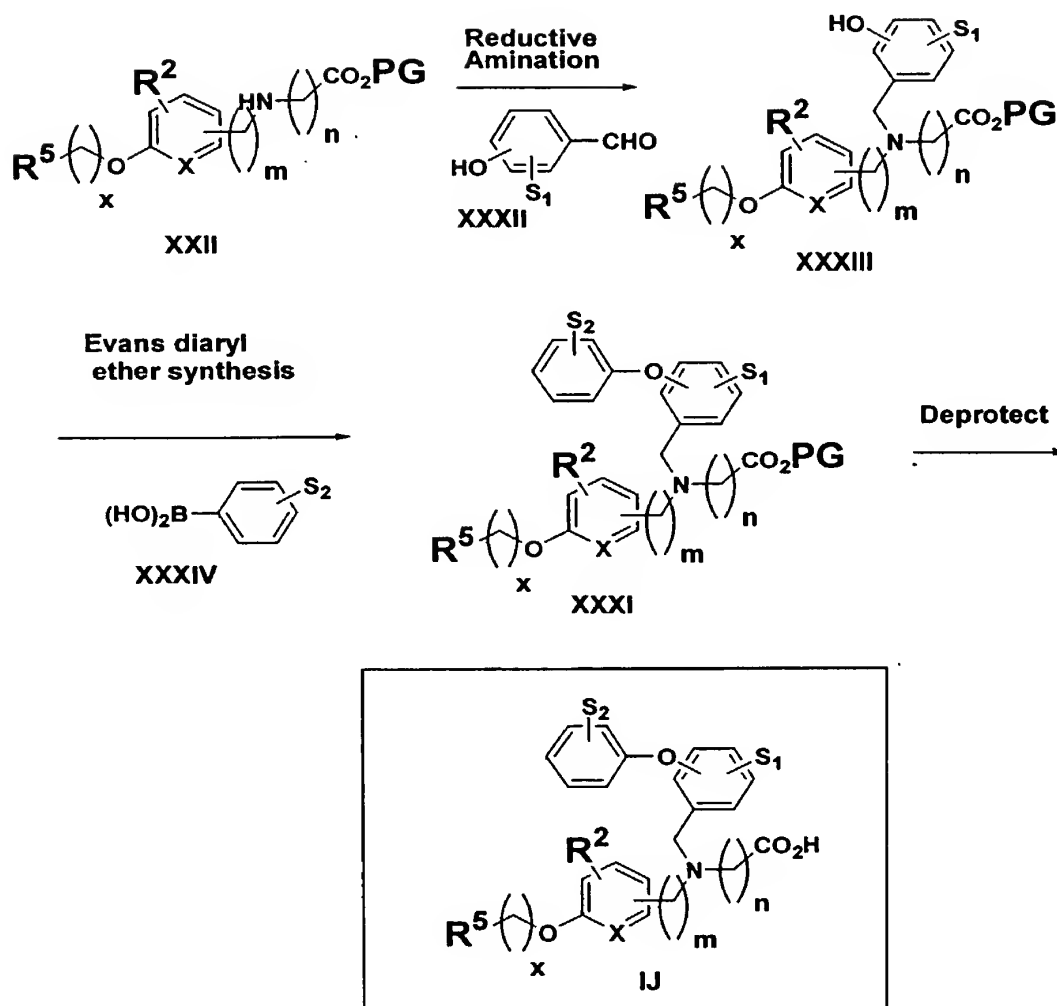


$(S_1 = \text{H, alkyl, halo, alkoxy, alkylthio, alkylamino, aryloxy, aryl, heteroaryl, alkoxy carbonyl, alkylaminocarbonyl})$   
 $S_2 = \text{H, alkyl, halo, alkoxy, alkylthio, alkylamino, aryloxy, aryl, heteroaryl, alkoxy carbonyl, alkylaminocarbonyl})$

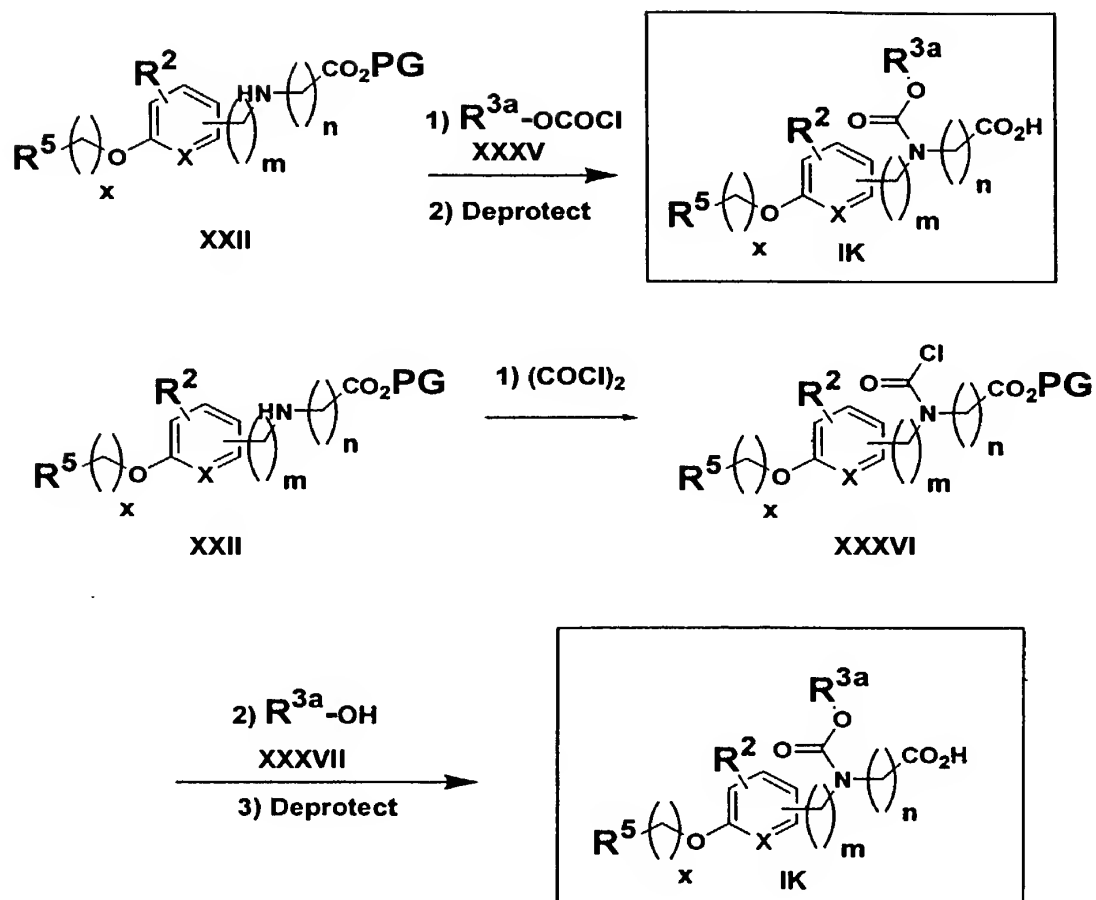
Scheme 8



Scheme 9

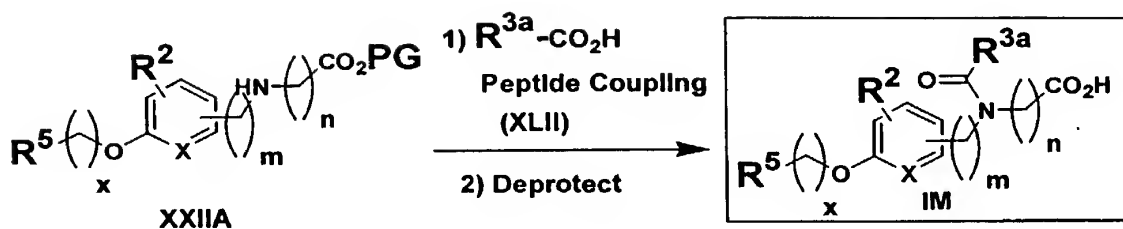


Scheme 10

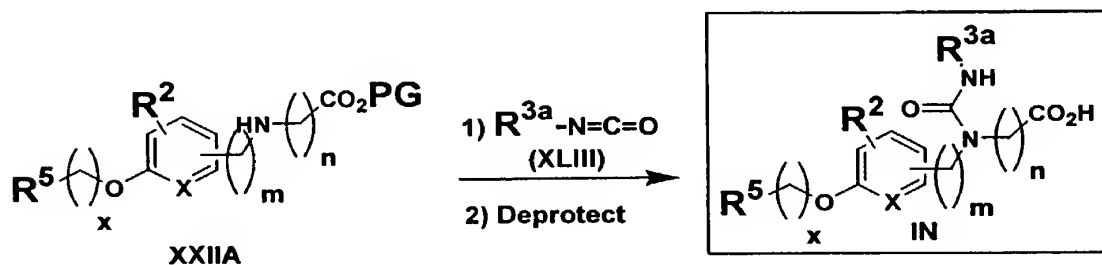


Scheme 11

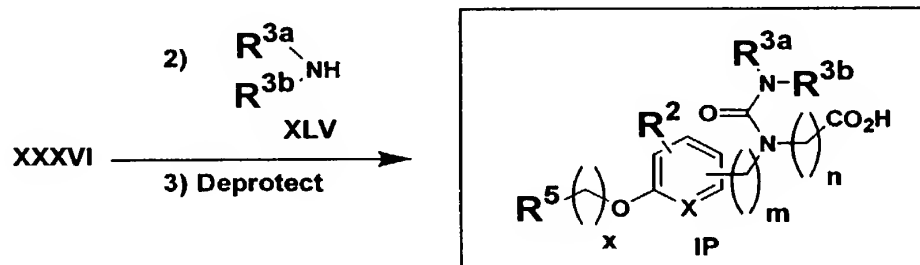
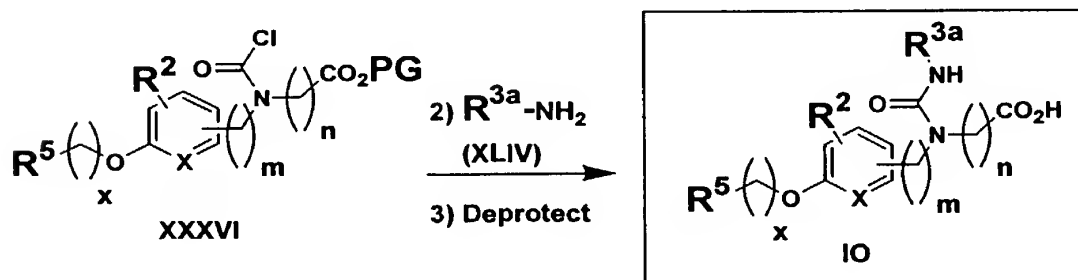




Scheme 13



Scheme 14

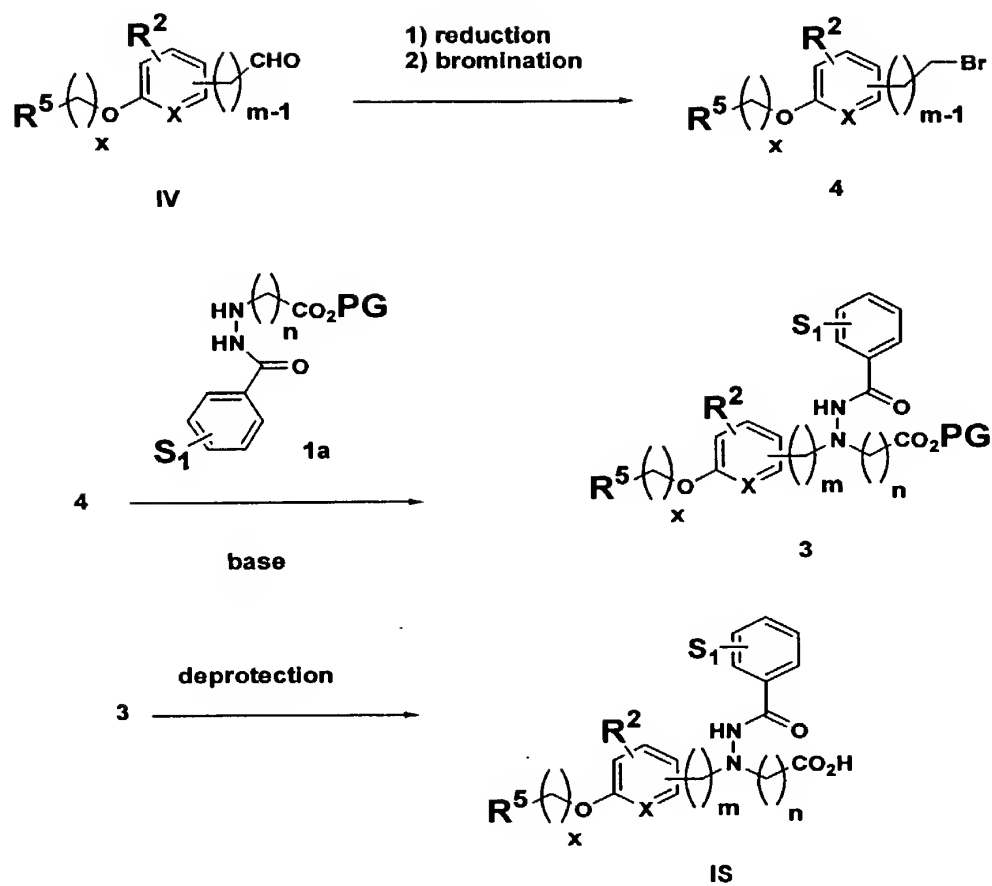


Scheme 15

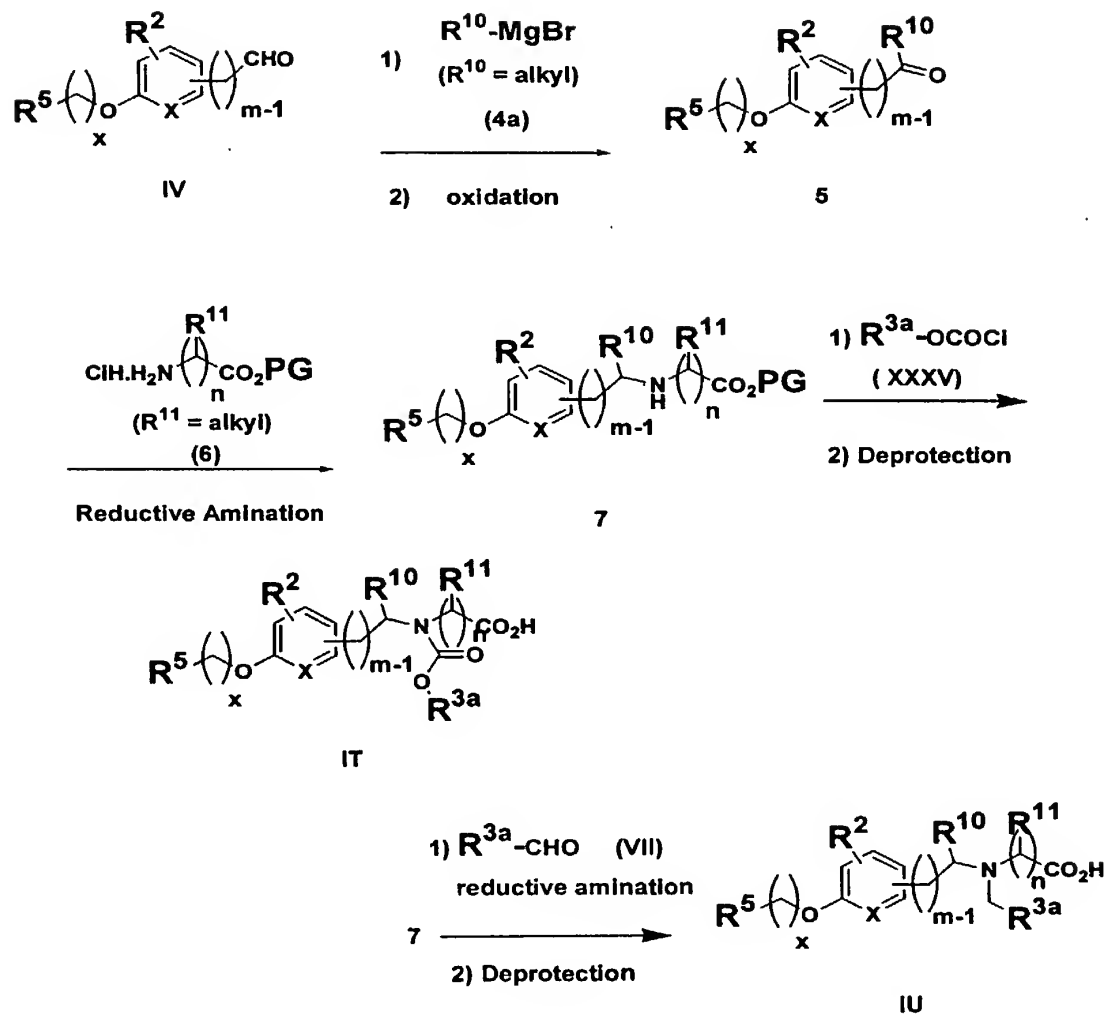




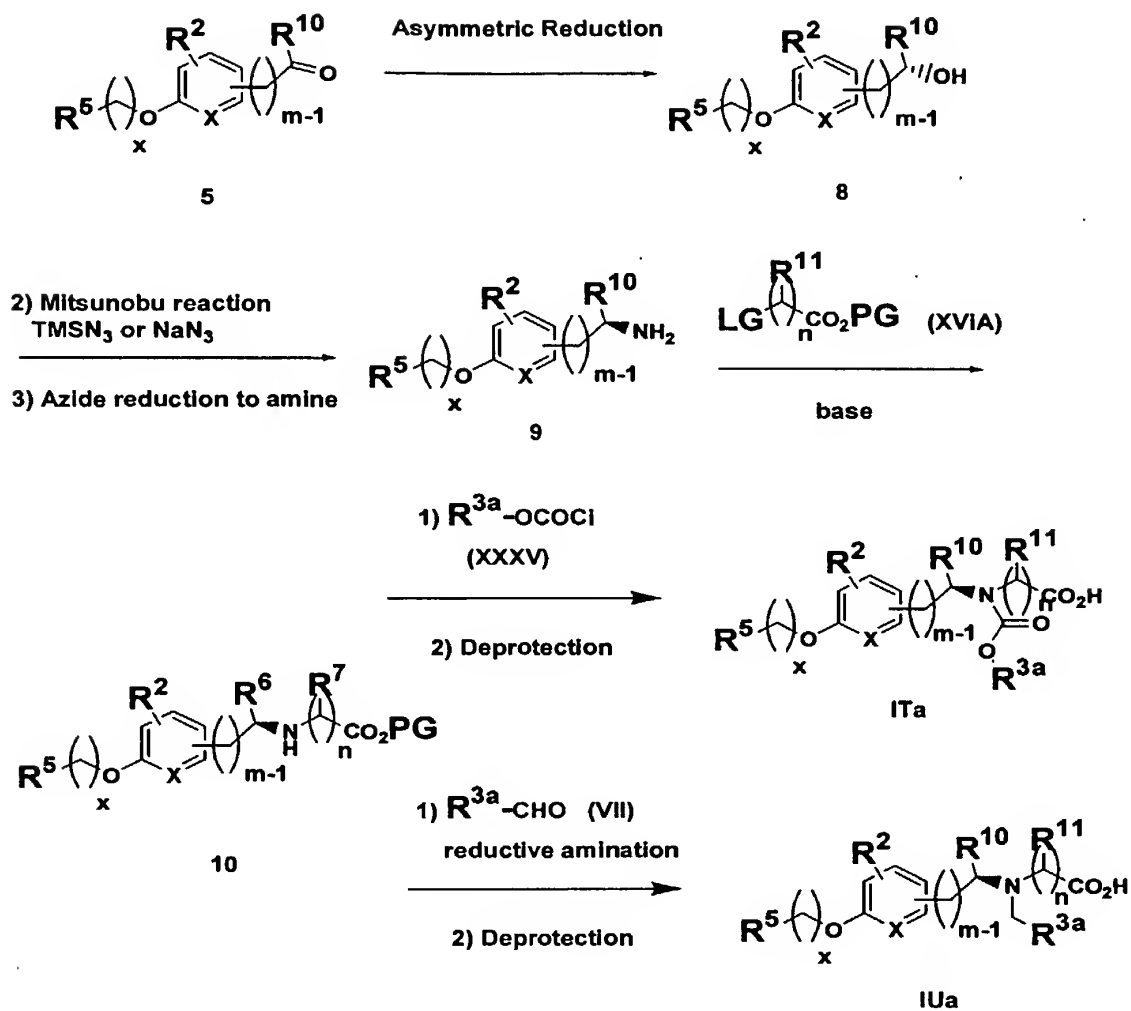




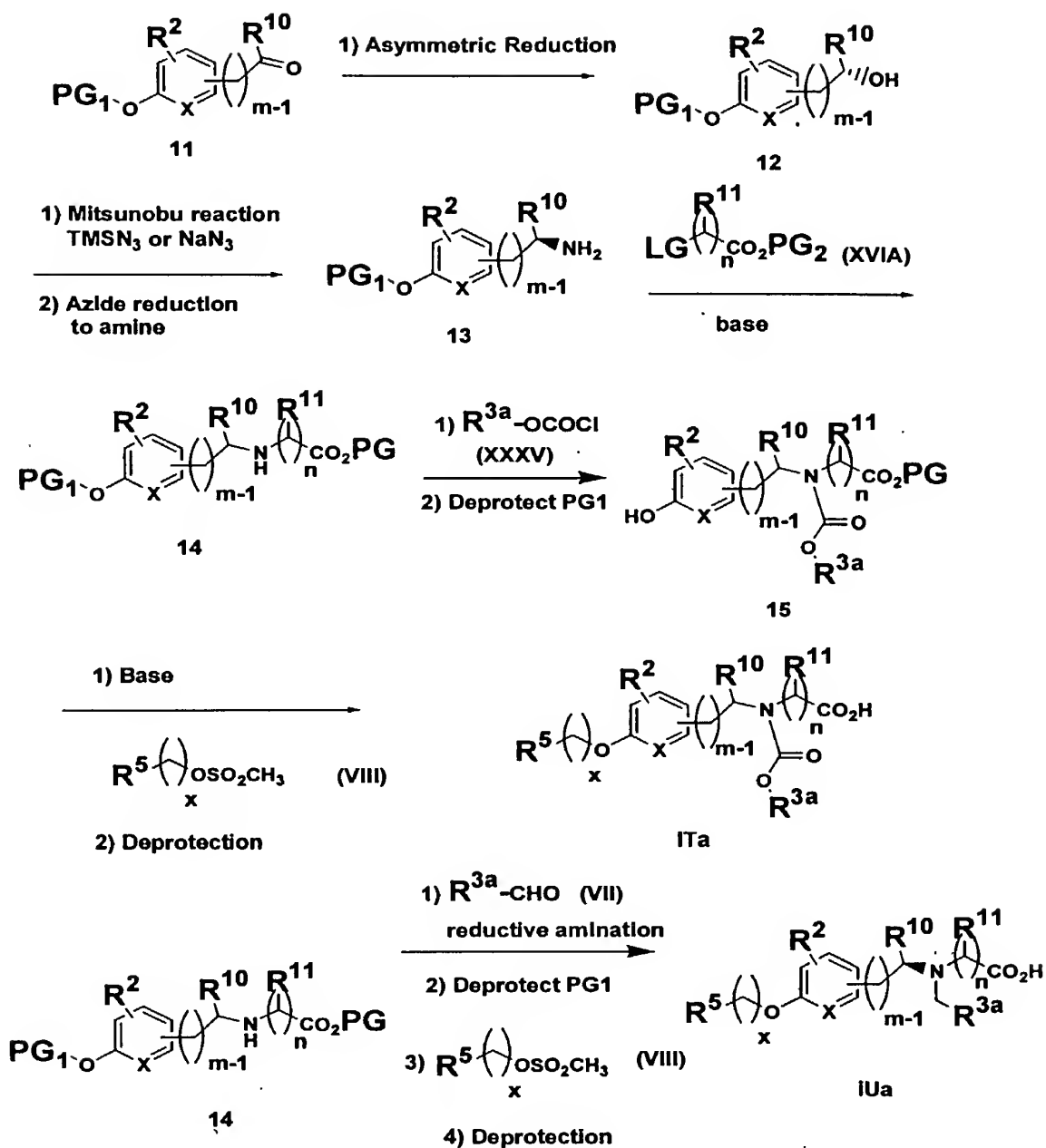
Scheme 19



Scheme 20



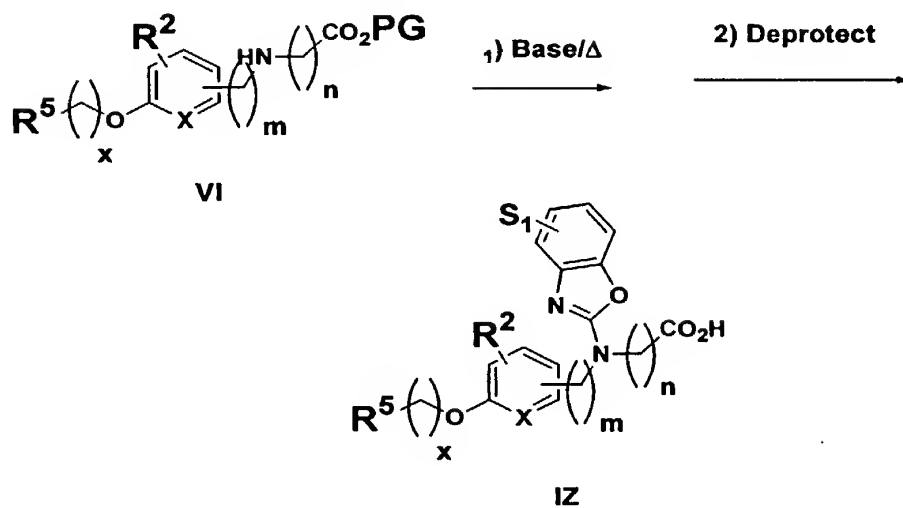
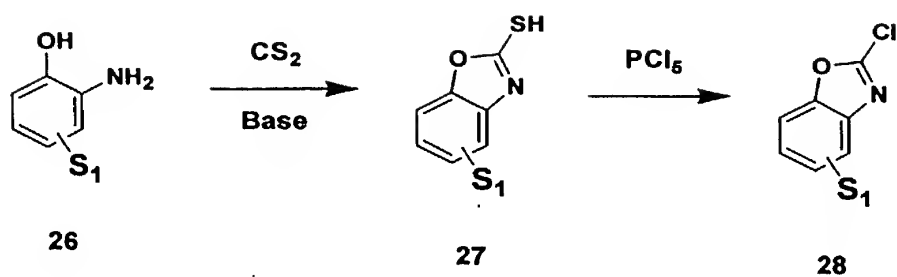
Scheme 21



Scheme 22



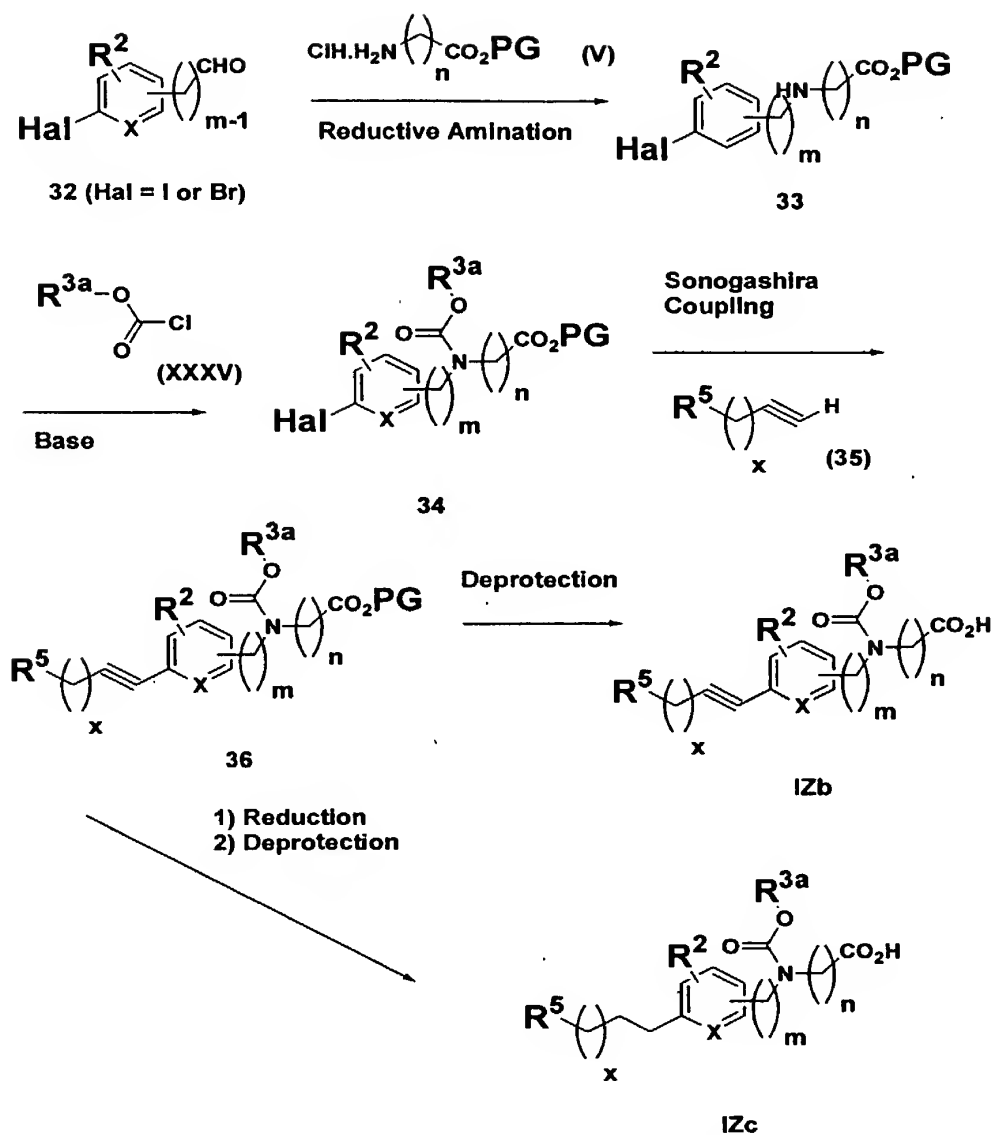




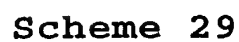
Scheme 25



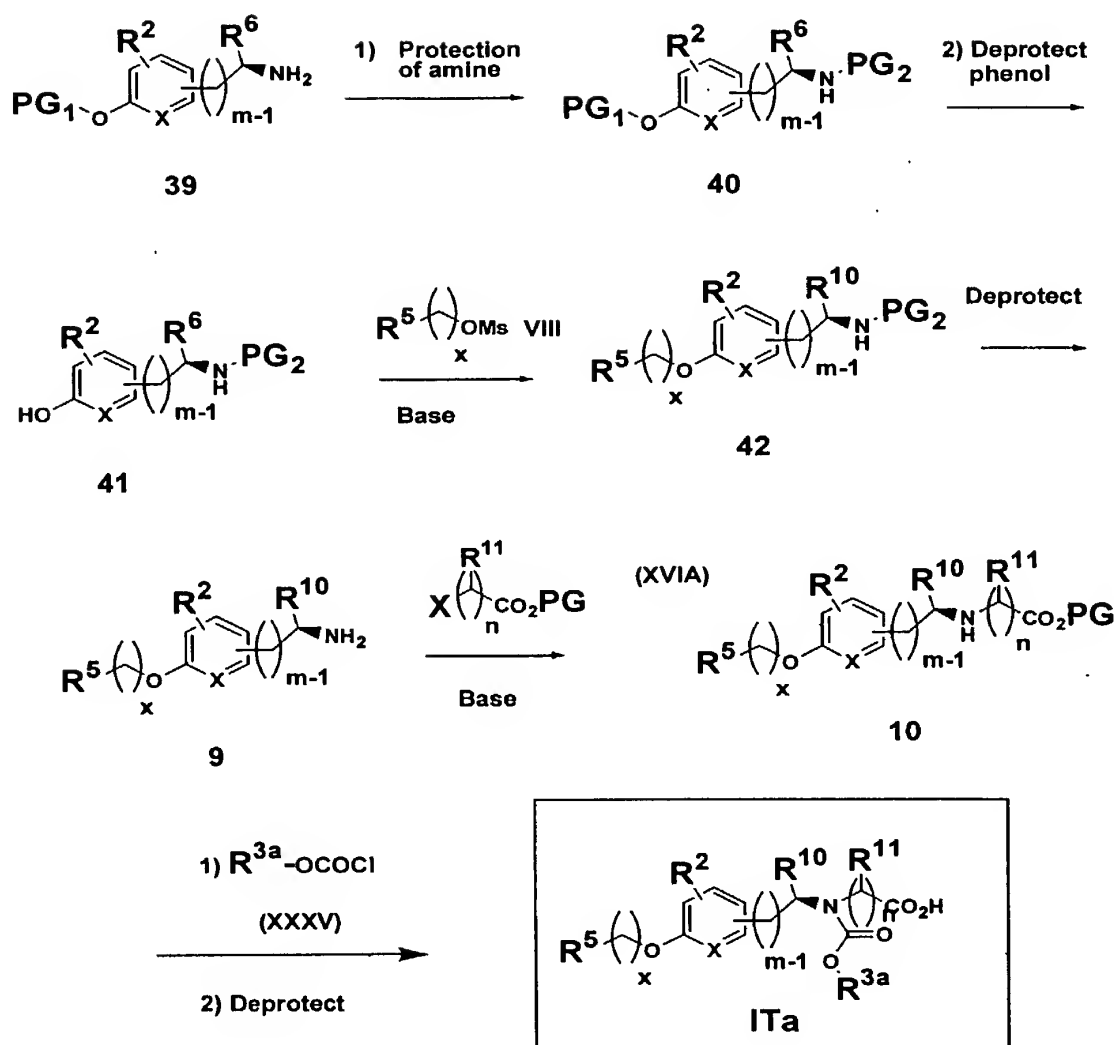




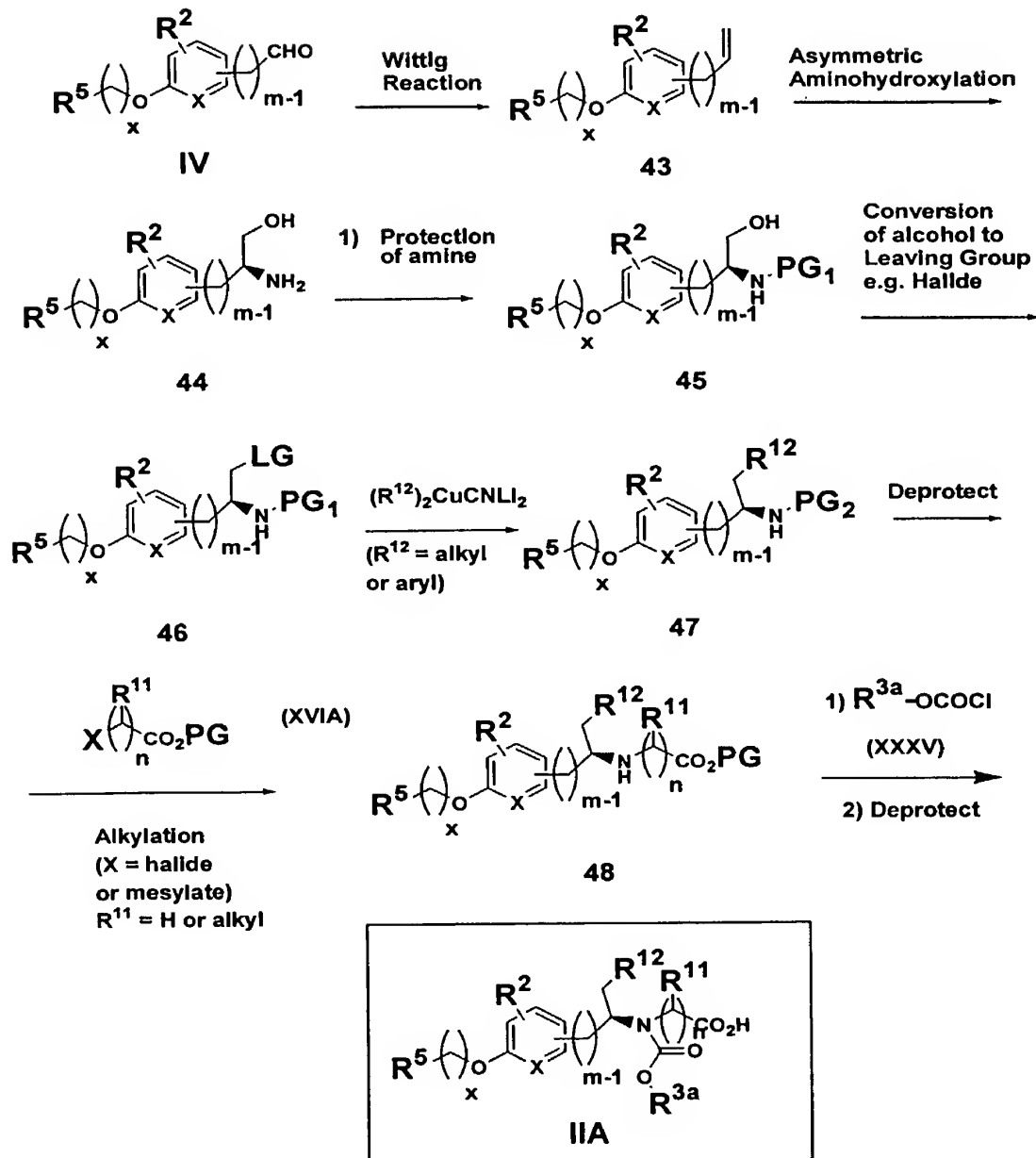
Scheme 27







Scheme 31



Scheme 32







hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio and/or any of the substituents for alkyl set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, and may optionally include an oxygen or nitrogen in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the substituents for alkyl set out herein.

The terms "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkenyl and alkynyl groups as described above having an aryl substituent.

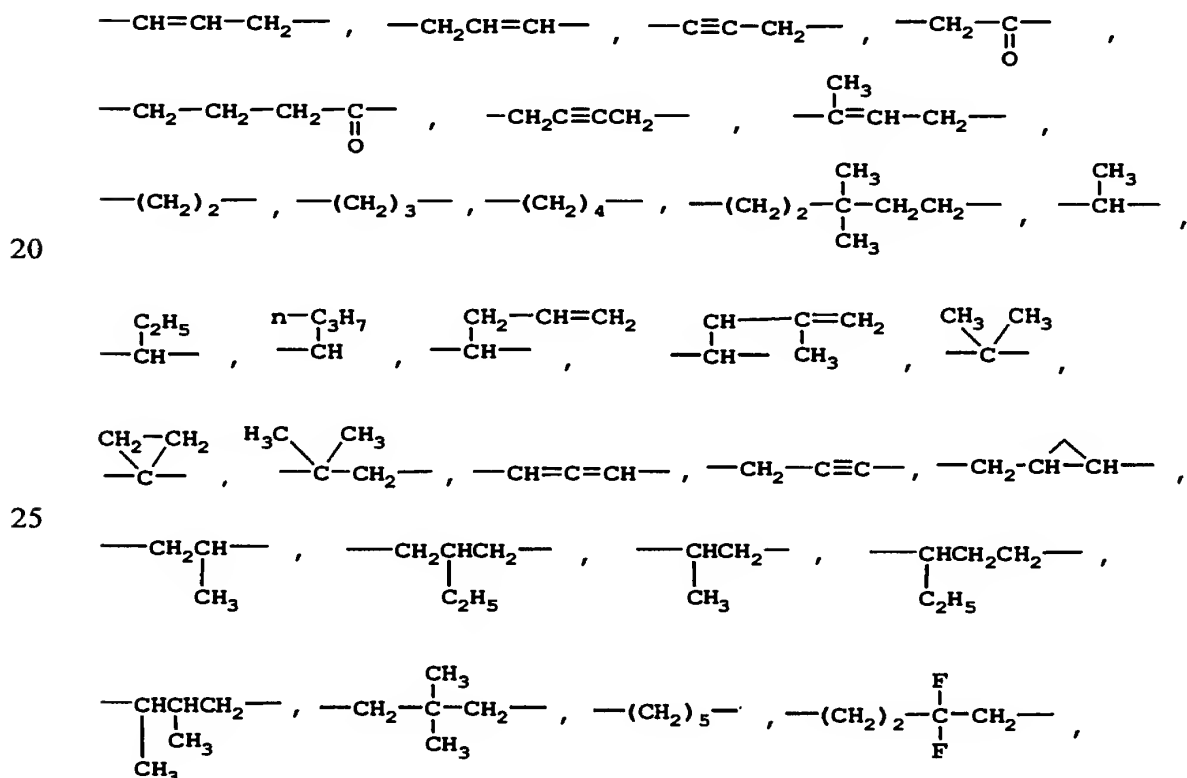
Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

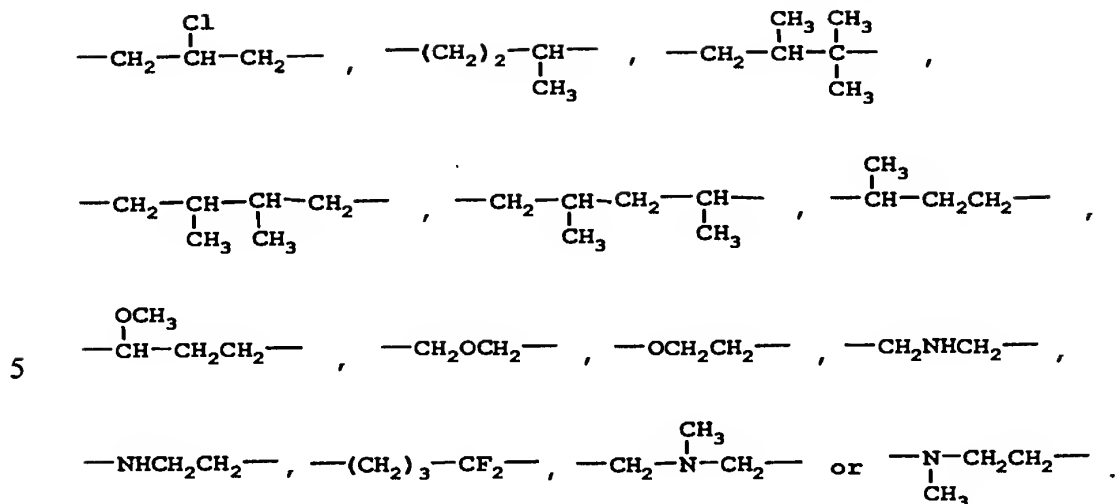
Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are

termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted as defined above for "alkenyl" and "alkynyl".

(CH<sub>2</sub>)<sub>x</sub>, (CH<sub>2</sub>)<sub>m</sub>, (CH<sub>2</sub>)<sub>n</sub> or (CH<sub>2</sub>)<sub>y</sub> includes alkylene, allenyl, alkenylene or alkynylene groups, as defined herein, each of which may optionally include an oxygen or nitrogen in the normal chain, which may optionally include 1, 2, or 3 substituents which include alkyl, alkenyl, halogen, cyano, hydroxy, alkoxy, amino, thioalkyl, keto, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, alkylcarbonylamino or alkylcarbonyloxy; the alkyl substituent may be an alkylene moiety of 1 to 4 carbons which may be attached to one or two carbons in the (CH<sub>2</sub>)<sub>x</sub> or (CH<sub>2</sub>)<sub>m</sub> or (CH<sub>2</sub>)<sub>n</sub> group to form a cycloalkyl group therewith.

15           Examples of  $(\text{CH}_2)_x$ ,  $(\text{CH}_2)_m$ ,  $(\text{CH}_2)_n$ ,  $(\text{CH}_2)_y$ ,  
alkylene, alkenylene and alkynylene include

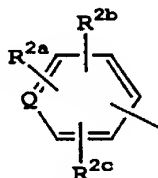




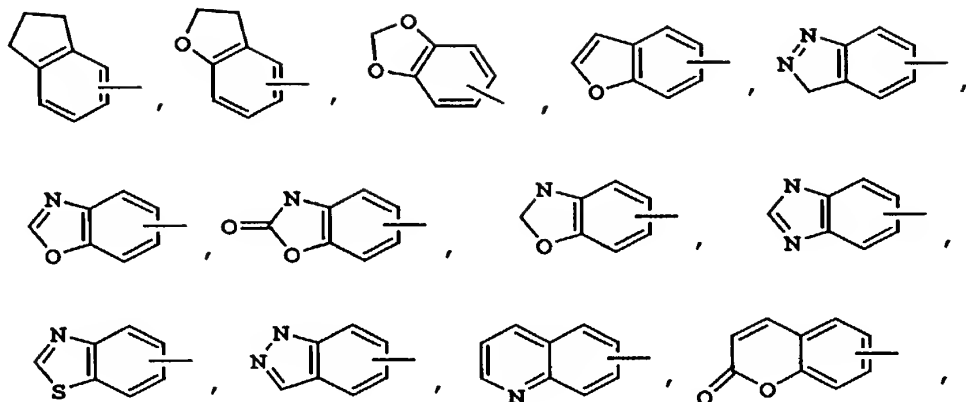
10 The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF<sub>3</sub>, with chlorine or fluorine being preferred.

15 The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

Unless otherwise indicated, the term "aryl" or the group



20 where Q is C, as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three  
 25 additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example



5

and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl and/or any of the substituents for alkyl set out herein.

Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

30

Unless otherwise indicated, the term "substituted amino" as employed herein alone or as part of another group refers to amino substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid and/or any of the substituents for alkyl as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

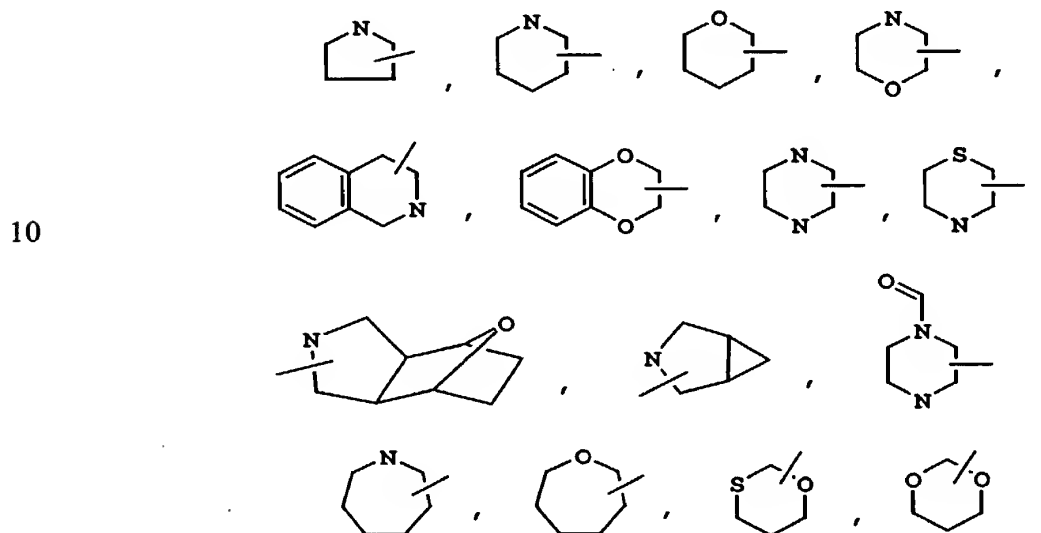
Unless otherwise indicated, the term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

Unless otherwise indicated, the term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

Unless otherwise indicated, the term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl  $\left( \begin{smallmatrix} \text{O} \\ \parallel \\ \text{C} \end{smallmatrix} \right)$  group; examples of acyl groups include any of the  $R^3$  groups attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

Unless otherwise indicated, the term "cycloheteroalkyl" as used herein alone or as part of

another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker  $(CH_2)_p$  (where p is 1, 2 or 3), such as

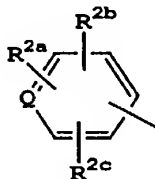


15

and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the substituents for alkyl or aryl set out herein. In addition, any of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

20

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring including



25

where Q is N, which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes



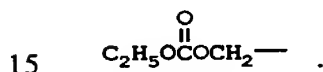
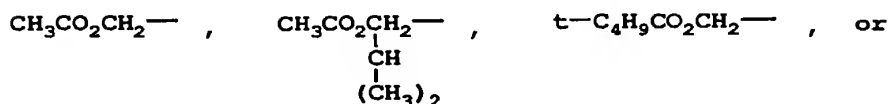
The term "prodrug esters" as employed herein includes prodrug esters which are known in the art for carboxylic and phosphorus acid esters such as methyl, ethyl, benzyl and the like. Other prodrug ester examples of  $R^4$  include the following groups:

(1-alkanoyloxy)alkyl such as,

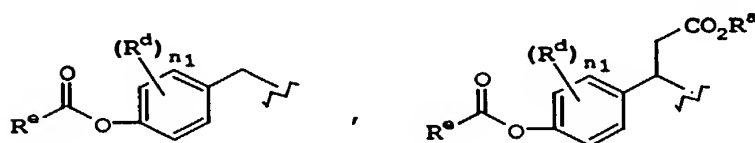
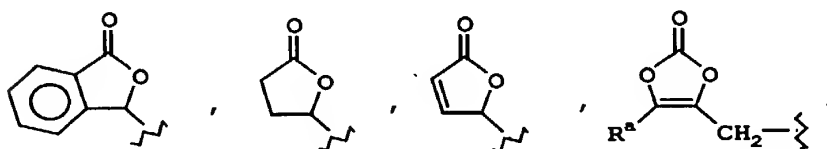


wherein  $R^a$ ,  $R^b$  and  $R^c$  are H, alkyl, aryl or arylalkyl; however,  $R^a\text{O}$  cannot be HO.

Examples of such prodrug esters  $R^4$  include



Other examples of suitable prodrug esters  $R^4$  include



wherein  $R^a$  can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl);  $R^d$  is H, alkyl, halogen or alkoxy,  $R^e$  is alkyl, aryl, arylalkyl or alkoxy, and  $n_1$  is 0, 1 or 2.

Where the compounds of structure I are in acid form they may form a pharmaceutically acceptable salt





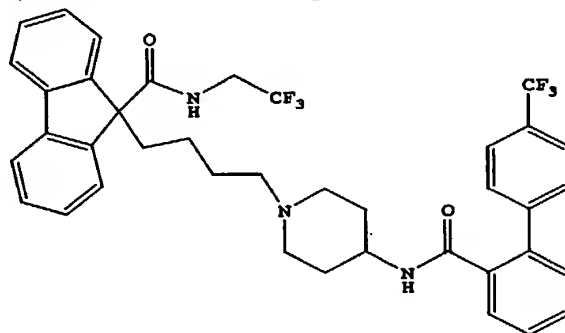
acid sequestrants, and/or nicotinic acid and derivatives thereof.

MTP inhibitors employed herein include MTP inhibitors disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Application Serial No. 09/175,180 filed October 20, 1998, now U.S. Patent No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

All of the above U.S. Patents and applications are incorporated herein by reference.

Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246.

The most preferred MTP inhibitor is 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and





U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

5 The hypolipidemic agent may be an ACAT inhibitor  
such as disclosed in, Drugs of the Future 24, 9-15  
(1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is  
effective in the prevention and regression of aortic  
fatty streak area in hamsters", Nicolosi et al,  
10 Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85;  
"The pharmacological profile of FCE 27677: a novel ACAT  
inhibitor with potent hypolipidemic activity mediated by  
selective suppression of the hepatic secretion of  
ApoB100-containing lipoprotein", Ghiselli, Giancarlo,  
15 Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a  
bioavailable alkylsulfanyl-diphenylimidazole ACAT  
inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett.  
(1996), 6(1), 47-50; "ACAT inhibitors: physiologic  
mechanisms for hypolipidemic and anti-atherosclerotic  
20 activities in experimental animals", Krause et al,  
Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Manfred  
A., Inflammation: Mediators Pathways (1995), 173-98,  
Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors:  
potential anti-atherosclerotic agents", Sliskovic et al,  
25 Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of  
acyl-CoA:cholesterol O-acyl transferase (ACAT) as  
hypocholesterolemic agents. 6. The first water-soluble  
ACAT inhibitor with lipid-regulating activity. Inhibitors  
of acyl-CoA:cholesterol acyltransferase (ACAT). 7.  
30 Development of a series of substituted N-phenyl-N'-[(1-  
phenylcyclopentyl)methyl]ureas with enhanced  
hypocholesterolemic activity", Stout et al, Chemtracts:  
Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho  
Pharmaceutical Co. Ltd).

35           The hypolipidemic agent may be an upregulator of  
LD2 receptor activity such as MD-700 (Taisho  
Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

5           The hypolipidemic agent may be an ileal  $\text{Na}^+$ /bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999).

The ATP citrate lyase inhibitor which may be employed in the combination of the invention may include, for example, those disclosed in U.S. Patent No. 5,447,954.

The above-mentioned U.S. patents are incorporated  
20 herein by reference. The amounts and dosages employed  
will be as indicated in the Physician's Desk Reference  
and/or in the patents set out above.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The dosages and formulations for the other  
35 hypolipidemic agent to be employed, where applicable,  
will be as set out in the latest edition of the  
Physicians' Desk Reference.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to  
5 four times daily.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about  
10 250 mg, one to four times daily.

For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin in dosages  
15 employed as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10  
20 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from  
25 about 0.5 to about 80 mg, and more preferably from about 1 to about 40 mg.

A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably  
30 from about 25 to about 200 mg.

The hypolipidemic agent may also be a lipoxxygenase inhibitor including a 15-lipoxxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613,  
35 isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly

selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

The compounds of formula I and the hypolipidemic agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin as well as niacin and/or cholestagel.

The other antidiabetic agent which may be optionally employed in combination with the compound of formula I may be 1,2,3 or more antidiabetic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents, preferably having a mechanism of action different from the compounds of formula I, which may include biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR  $\gamma$  agonists, such as thiazolidinediones, PPAR $\alpha$  agonists such as fibric acid derivatives,  $\alpha$ P2 inhibitors, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, meglitinides, insulin, and/or glucagon-like peptide-1 (GLP-1).

The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

Where the antidiabetic agent is a biguanide, the compounds of structure I will be employed in a weight



ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as  
5 glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the  $\beta$ -cells, with glyburide and glipizide being preferred,  
10 which may be administered in the same or in separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.02:1 to  
15 about 5:1.

The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the  
20 same or in a separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 10:1.

25 The compounds of structure I may be employed in combination with a PPAR  $\gamma$  agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin<sup>®</sup>, disclosed in U.S. Patent No.  
30 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer,  
35 isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or

YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

5 The compounds of structure I will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

10 The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of structure I.

15 The compounds of structure I may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), as well as AC2993 (Amylin) and LY-315902 (Lilly), which may be administered via injection, intranasal, inhalation or by transdermal or buccal devices.

20 Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyrider, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in  
25 formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

30 Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

35 Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are

5 incorporated herein by reference.

The other antidiabetic agent may also be a PPAR  $\alpha/\gamma$  dual agonist such as AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin  
10 Sensitizer Acts As a Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998).

15 The antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. provisional application No. 60/158,773, filed October 12, 1999 (attorney file LA49), employing dosages as set out therein. Preferred are the compounds designated as preferred in the above  
20 application.

The antidiabetic agent may be an  $\alpha P2$  inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. provisional application No. 60/127,745, filed April 5,  
25 1999 (attorney file LA27\*), employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The antidiabetic agent may be a DP4 inhibitor such as disclosed in Provisional Application 60/188,555 filed  
30 March 10, 2000 (attorney file LA50), WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) (preferred) as  
35 disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (disclosed by Yamada et

5

10

15

20

25

30

35

The thyroid receptor agonist which may be optionally employed in combination with a compound of formula I may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio), GB98/284425 (KaroBio), and U.S. Provisional Application 60/183,223 filed February 17, 2000, with compounds of the KaroBio applications and the above U.S. provisional application being preferred.

The anorectic agent which may be optionally employed in combination with a compound of formula I may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

The various anti-obesity agents described above may be employed in the same dosage form with the compound of formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

The antihypertensive agents which may be employed in combination with the compound of formula I of the invention include ACE inhibitors, angiotensin II receptor antagonists, NEP/ACE inhibitors, as well as calcium channel blockers,  $\beta$ -adrenergic blockers and other types of antihypertensive agents including diuretics.

The angiotensin converting enzyme inhibitor which may be employed herein includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in U.S. Pat. No. 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906 with zofenopril being preferred.

Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril and YS980.

Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in European Patent Application Nos. 80822 and 60668; Chugai's MC-838 disclosed in C.A. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[ (1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U.S. Pat. No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in Euro. Patent No. 79-022 and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in Arzneimittelforschung 34:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987); R 31-2201 (Hoffman-LaRoche) disclosed in FEBS Lett. 165:201 (1984); lisinopril (Merck), indalaprill (delapril) disclosed in U.S. Pat. No. 4,385,051; indolapril (Schering) disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983), spirapril (Schering)

5

10

15

30

35

5 more preferably from about 10 to about 150 mg.

10 mg/kg to about 1 mg/kg.

conventional carriers.

15 It will be appreciated that preferred dosages of ACE inhibitor and AII antagonist as well as other antihypertensives disclosed herein will be as set out in the latest edition of the Physician's Desk Reference (PDR).

20 Other examples of preferred antihypertensive agents  
suitable for use herein include omapatrilat (Vanlev®)  
amlodipine besylate (Norvasc®), prazosin HCl  
(Minipress®), verapamil, nifedipine, nadolol, diltiazem,  
felodipine, nisoldipine, isradipine, nicardipine,  
25 atenolol, carvedilol, sotalol, terazosin, doxazosin,  
propranolol, and clonidine HCl (Catapres®).

torasemide, furosemide, spironolactone; and indapamide.

30        Antiplatelet agents which may be employed in combination with compounds of formula I of the invention include aspirin, clopidogrel, ticlopidine, dipyridamole, abciximab, tirofiban, eptifibatide, anagrelide, and ifetroban, with clopidogrel and aspirin being preferred.

35           The antiplatelet drugs may be employed in amounts  
as indicated in the PDR. Ifetroban may be employed in  
amounts as set out in U.S. Patent No. 5,100,889.





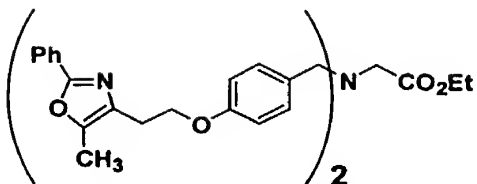






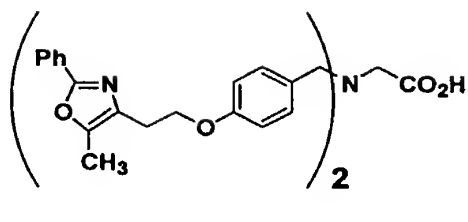




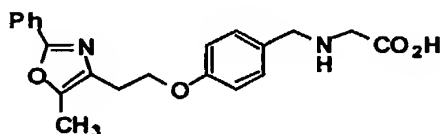


To a solution of Example 1 Part A compound (147 mg;  
5 0.479 mmol) and glycine ethyl ester hydrochloride (73 mg;  
0.52 mmol) in DCE (2 mL) was added  $\text{Et}_3\text{N}$  and  $\text{NaBH}(\text{OAc})_3$   
(156 mg; 0.74 mmol) and the reaction was stirred  
overnight at RT. Flash chromatography (stepwise gradient  
from 7:3 to 2:3 hex: EtOAc) gave 35 mg (21%) of the  
10 dibenzyl glycine ester (Example 2 Part A compound). In  
addition, 127 mg (67%) of the monobenzyl glycine ester  
(Example 3 Part A compound) was obtained.

B.

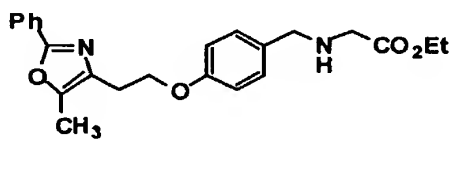


5        A solution of Example 1 Part A compound (35 mg;  
0.051 mmol) in MeOH (2 mL) and aqueous NaOH (3 mL of a 1M  
solution) was heated under reflux for 12 h. The solution  
was adjusted to pH 5 with aqueous 1M HCl and aqueous 1 M  
NaOH, then extracted with EtOAc (3x). The combined  
10    organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>),  
and concentrated in vacuo to give title compound (13 mg)  
as a colorless solid. [M + H]<sup>+</sup> = 658.2

Example 3

15

A.




20

To a solution of Example 1 Part A compound (147 mg;  
0.479 mmol) and glycine ethyl ester hydrochloride (73 mg;  
mmol) in DCE was added Et<sub>3</sub>N and NaBH(OAc)<sub>3</sub> (156 mg; 0.74  
mmol). Flash chromatography (stepwise gradient from 7:3  
25    to 2:3 hex: EtOAc) gave 127 mg (67%) of the title  
compound. In addition, 35 mg (21%) of the bis-benzyl  
glycine ester (Example 2 Part A compound) was obtained as  
a byproduct.

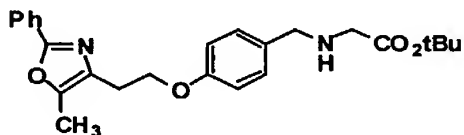


CC1=C(C(=N1C2=CC=CC=C2)COC3=CC=C(C=C3)CNCC(=O)O)C

Example 4



A solution of the amino t-butyl ester (0.040 g, 0.095 mmol), (prepared as described for Example 7 Part C, except that the aldehyde used in the reductive amination was Example 1 Part A instead of Example 7 Part A)

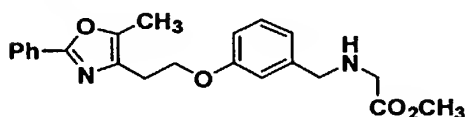


- 93 -

5

CC1=C(CCOc2ccc(cc2)CN(Cc3ccccc3)c4ccccc4O1)c5ccccc5C(=O)O

A solution of 2-chlorobenzoxazole (20 mg; 0.131 mmol), the secondary amine-methyl ester (52 mg; 0.146 mmol)

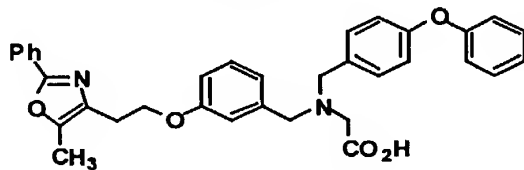


25

10

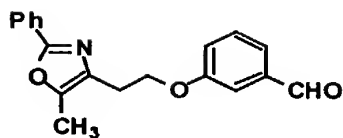
CC1=C(C(=N1C2=CC=CC=C2)OCCOC3=CC=C(C=C3)CN(C3)CC(=O)O)C4=CC=CC=C4COC(=O)CNCCc1ccc(OCCc2c(C)c(Oc3ccccc3N2)c4ccccc4)cc1

### Example 7



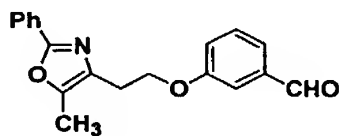
- 95 -

A.



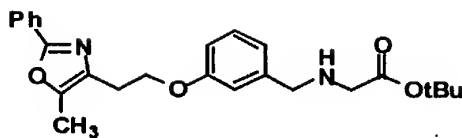
5 To a 0°C solution of 3-hydroxybenzaldehyde (3.00 g; 24.6 mmol), 2-phenyl-5-methyl-oxazole-4-ethanol (5.00 g; 24.6 mmol) and Ph<sub>3</sub>P (7.10 g; 27.1 mmol) in dry THF (75 mL) was added dropwise DEAD (4.27 mL; 27.1 mmol) over 10 min. The brown-orange solution was allowed to warm to RT and stirred at RT for 24 h. The solution was concentrated *in vacuo* and chromatographed (SiO<sub>2</sub>; stepwise gradient: 100% hex to hex:EtOAc 3:1) to give Part A compound as a pale yellow viscous oil (4.01 g; 53%).

15 A.1. Alternative Procedure for Preparing Part A Aldehyde



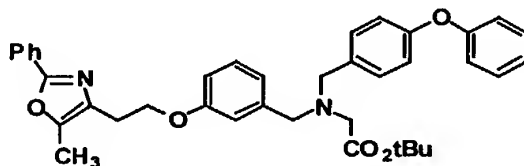
20 To a solution of 3-hydroxybenzaldehyde (9.1 g; 0.074 mmol) in CH<sub>3</sub>CN (206 mL) was added K<sub>2</sub>CO<sub>3</sub> (10.3 g). The mixture was heated to 90°C in an oil bath and stirred for 18 h at 90°C (the reaction was complete at this point by analytical HPLC). The reaction was cooled to RT, then  
25 diluted with EtOAc (500 mL), washed with H<sub>2</sub>O, aqueous NaOH (2 x 100 mL of a 1 M solution) and brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residual oil was chromatographed (SiO<sub>2</sub>; hex:EtOAc from 9:1 to 4:1) to give the Part A aldehyde (12.7 g; 67%) as a  
30 viscous, clear, pale yellow oil.

B.



5        A solution of the Part A1 compound (4.00 g; 13.0 mmol), glycine tert-butyl ester hydrochloride (2.40 g; 14.3 mmol) and Et<sub>3</sub>N (2.18 mL; 15.7 mmol) in MeOH (30 mL) was stirred at RT for 6 h and then cooled to 0°C. A solution of NaBH<sub>4</sub> (594 mg; 15.7 mmol) in MeOH (10 mL) was  
10 added portionwise at 0°C to the solution of crude imine over ~15 min. The solution was stirred at 0°C for 3 h, then at RT for 3 h, then concentrated *in vacuo* without heating to removed MeOH. The residue was partitioned between saturated aqueous NaCl and EtOAc (50 mL each).  
15 The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give a yellow oil, which was chromatographed on SiO<sub>2</sub> (stepwise gradient; hex:EtOAc from 4:1 to 2:3) to give Part B compound as a pale  
20 viscous yellow oil (4.82 g; 88%).

C.

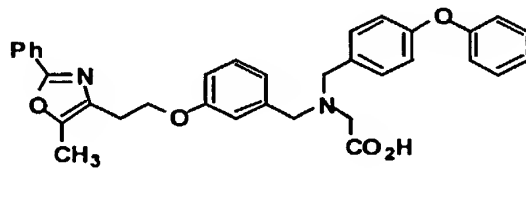


25

To a solution of Part B compound (0.400 g; 0.95 mmol) and 4-phenoxybenzaldehyde (0.216 g; 1.09 mmol) in DCE (5 mL) was added NaBH(OAc)<sub>3</sub> (0.300 g; 1.42 mmol), followed by HOAc (25 µL). The reaction was stirred at RT  
30 for 24 h. 10% unreacted starting amine was still present by analytical HPLC. Additional aldehyde (30 mg) and

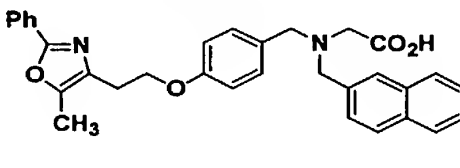
5

D.

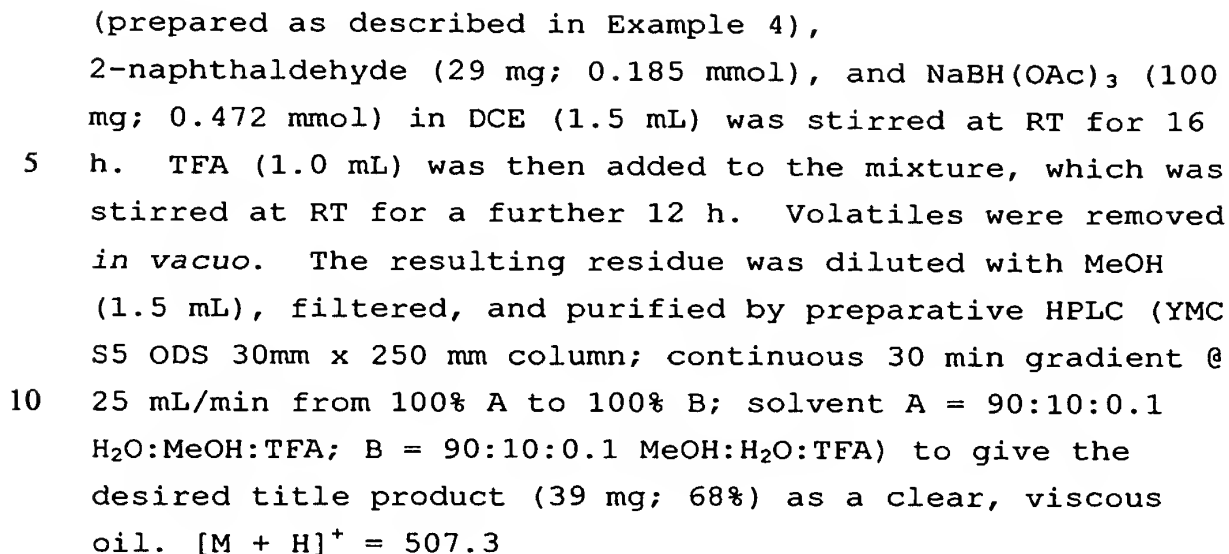


20

### Example 8



30



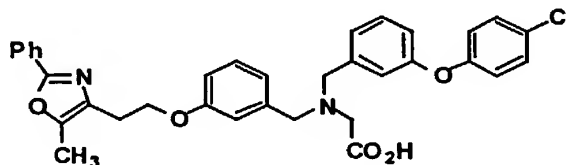
## 15

CCOC(=O)CNCc1ccc(OCCc2c(C)c(O)c(NC3=CC=CC=C3)c2)cc1

- 99 -

the residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and eluted through solid  $\text{NaHCO}_3$  (to remove excess TFA) with excess  $\text{CH}_2\text{Cl}_2$ . The combined filtrates were concentrated *in vacuo* to provide the desired amino acid Part A compound (1.48 g; 95%).  $[\text{M} + \text{H}]^+ = 457.2$

B.



10

The title compound was prepared as part of a solution phase library run using the following exemplary procedure:

To a solution of the Part A amino acid compound (27 mg, 0.074 mmol; in 2 mL  $\text{CH}_2\text{Cl}_2$ ) was added (4-chlorophenoxy)-3-benzaldehyde (86 mg; 0.37 mmol),  $\text{NaBH}(\text{OAc})_3$  (79 mg, 0.37 mmol) and HOAc (0.1 mL). The reaction was stirred at RT for 15 h.

The product was purified via solid-phase extraction using a Varian SAX cartridge (3 g of sorbent in a 6 mL column, 0.3 meq/g) by the procedure outlined below:

- 1) The column was conditioned with MeOH (10 mL) and  $\text{CH}_2\text{Cl}_2$  (20 mL)
- 2) The reaction mixture was loaded onto the SAX column
- 3) The column was rinsed with  $\text{CH}_2\text{Cl}_2$  (10 mL)
- 4) The column was rinsed with 1% TFA in MeOH (3 mL)
- 5) The product was eluted with 1% TFA in MeOH (20 mL)



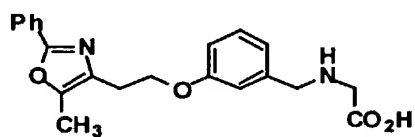
10

(procedure used with heterocyclic aldehydes)



20

A mixture of the amino acid (14 mg; 0.038 mmol),



25

5 68%) as a clear, viscous oil.

CC1=C(C(=N1C2=CC=CC=C2)OC3=CC=CC=C3)CCOC4=CC=CC=C4CN(CCC(=O)O)Cc5cc(oc5C6=CC=CC=C6Cl)C7=CC=CC=C7

An alternative purification procedure to preparative HPLC was used as follows:

15 Chemicals; 3 g of sorbent in a 6 mL column, 0.3 meq/g) by  
the procedure outlined below:

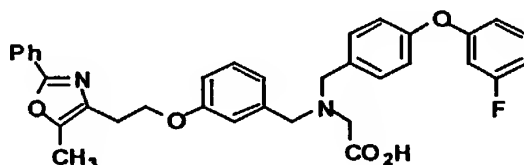
- 20

30

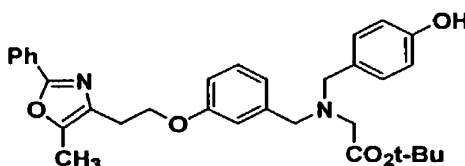
product-containing fractions were concentrated *in vacuo* using a Speed Vac to give the desired title product.

Reverse Phase HPLC analysis (YMC S5 ODS 4.6 x 33 mm column, continuous gradient from 100% A to 100%B for 2 min at a flow rate of 5 mL/min [Solvent A=10% MeOH/90% H<sub>2</sub>O/0.2% H<sub>3</sub>PO<sub>4</sub>; Solvent B = 90% MeOH/10% H<sub>2</sub>O/0.2% H<sub>3</sub>PO<sub>4</sub>]) indicated that the product purity was 92%. In addition, LC/MS (electrospray) gave the correct molecular ion [(M+H)<sup>+</sup> = 583] for title compound.

10

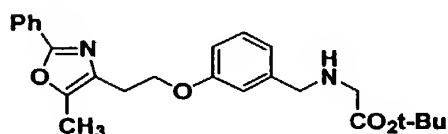
Example 11

A.



15

To a mixture of the amino-tert-butyl ester (0.339 g, 0.80 mmol),

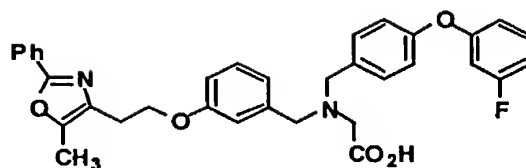


20

(prepared as described in Example 7, Part B), 4-hydroxybenzaldehyde (0.127 g, 1.03 mmol) and NaBH(OAc)<sub>3</sub> (0.510 g, 2.4 mmol) was added 7 drops of HOAc. The reaction was stirred at RT for 16 h. The mixture was diluted with EtOAc, then washed with aqueous NaHCO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The crude product was chromatographed (SiO<sub>2</sub>; hexanes/EtOAc 3:1 to 1:4) to provide the 4-hydroxybenzyl amino ester title compound (0.381 g, 90%).

25

B.



5

The title compound was prepared as part of a solution phase library run using the following exemplary procedure.

To a solution of Part A phenol compound (30 mg, 0.057 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was added 3-fluorophenyl boronic acid (12 mg; 0.086 mmol) and 4A molecular sieves (pre-dried at  $400^\circ\text{C}$  overnight) at RT. After stirring for 5 min,  $\text{Cu}(\text{OAc})_2$  (1 eq),  $\text{Et}_3\text{N}$  (5 eq) and pyridine (5 eq) were added to the mixture. The vial was capped and air was allowed to pass into the reaction. The reaction was stirred at RT for 60 h and was complete by analytical HPLC and LC/MS. (For other reactions which were incomplete after this time, additional boronic acid (1.5 equivalent) was added in order to form additional desired product). The reaction mixture was filtered and concentrated *in vacuo*.

The product was purified via solid-phase extraction using a United Technology SCX column (2 g of sorbent in a 6 mL column) by the procedure outlined below.

25

1) The column was conditioned with MeOH (10 mL) and  $\text{CH}_2\text{Cl}_2$  (10 mL)

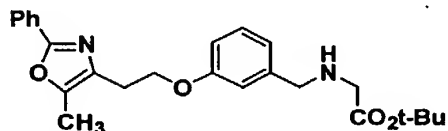
2) The residue was dissolved in a minimal volume of  $\text{CH}_2\text{Cl}_2$  and loaded onto the SCX column.

30

3) The cartridge was successively washed with  $\text{CH}_2\text{Cl}_2$  (20 mL),  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (20% MeOH, 20 mL) and MeOH (20 mL)

5 The product-containing fractions were concentrated  
in *vacuo* to give the desired tert-butyl ester. (Some  
incomplete reactions required chromatography (on SiO<sub>2</sub>) of  
the crude material to give esters of the requisite  
purity). The t-butyl ester was treated with a solution  
10 of 30% TFA in CH<sub>2</sub>Cl<sub>2</sub> overnight. Volatiles were removed  
and the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and  
concentrated in *vacuo* on a Speed Vac to afford the  
desired title product (30 mg; 77%). Reverse phase HPLC  
analysis indicated that the product purity was 90%. In  
15 addition LC/MS gave the correct molecular ion [(M+H)<sup>+</sup> =  
567] for the desired title compound.

## 20



- 105 -

5

10



15

20

25

30

2) The residue was dissolved in a minimal volume of  $\text{CH}_2\text{Cl}_2$  and loaded onto the SCX column.

5 4) The product was eluted with a solution of 0.5N  $\text{NH}_3$  in  
MeOH.

10

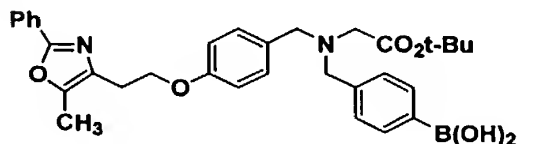
15

8) The product-containing fractions were collected and concentrated in vacuo to give the purified tert-butyl ester

25 Reverse phase HPLC analysis indicated that the product  
purity was 91%. In addition LC/MS gave the correct  
molecular ion  $[(M+H)^+ = 563.2]$  for the desired compound.

Cc1c(Cc2ccc(OCCN(Cc3ccc(cc3)C4=CC=CC=C4)C(=O)O)cc2)oc2c(c1)nc(c2)c3ccccc3

To a solution of 3-bromopyridine (32 mg; 0.2 mmol) in DME (1 mL) were successively added  $(\text{Ph}_3\text{P})_4\text{Pd}$  (5 mg; 0.05 mol equiv) and the Example 12 Part A boronic acid (50 mg; 0.09 mmol)



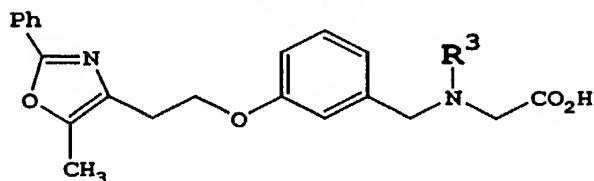
The reaction mixture was filtered and the filtrate was chromatographed on a silica gel cartridge (2 mL; EtOAc). The product-containing fractions were concentrated *in vacuo* and the residue was chromatographed on another silica gel cartridge (2 mL; stepwise gradient of hexanes, hex:EtOAc 3:1 and EtOAc). The product-containing fractions were concentrated *in vacuo* and the residue was eluted through an SCX (2 g) cartridge (20 mL each of CH<sub>2</sub>Cl<sub>2</sub> and MeOH; then product eluted with 2M ammonia in MeOH). The product-containing fractions were concentrated *in vacuo* to give the desired biaryl amine tert-butyl ester product. This was treated with a solution of CH<sub>2</sub>Cl<sub>2</sub>/TFA (7:3; 1 mL) overnight for 14 h. Volatiles were removed to give title compound (39 mg; 67%) as an oil.  $[M + H]^+ = 534.3$



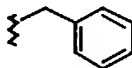
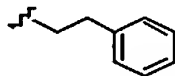
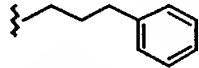
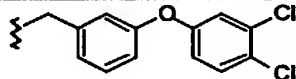
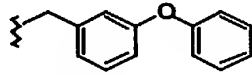
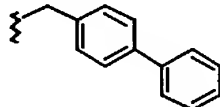
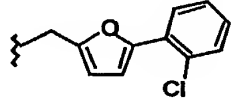
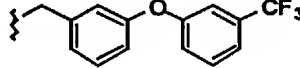
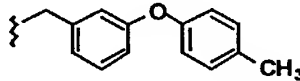
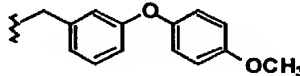
## Examples 14 to 124

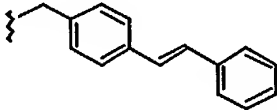
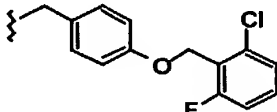
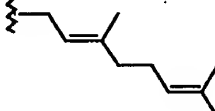
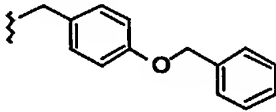
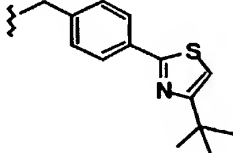
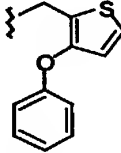
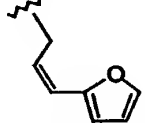
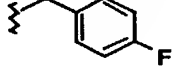
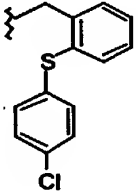
Following one of the above procedures, the following compounds of the invention were prepared:

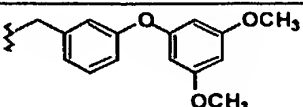
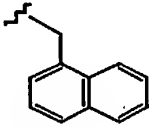
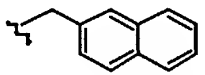
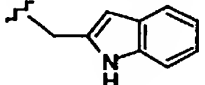
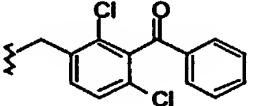
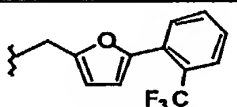
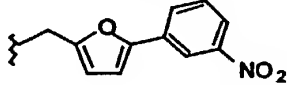
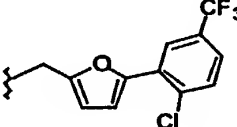
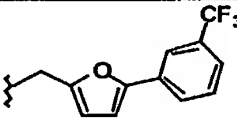
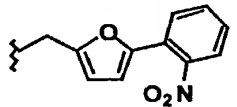
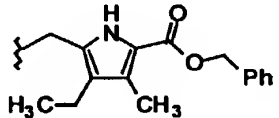
### Table 1

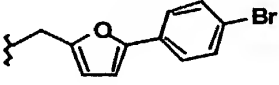
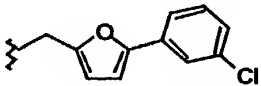
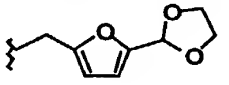
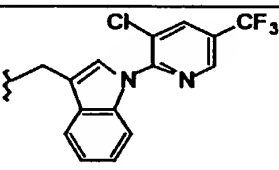
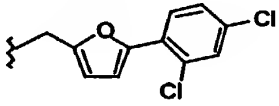
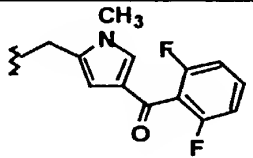
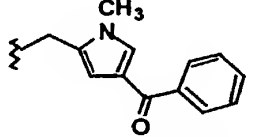
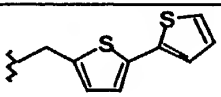
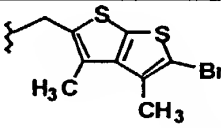
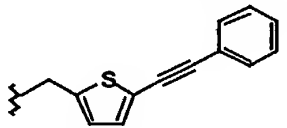


5

Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
14		457.3
15		471.3
16		485.3
17		617.2
18		549.3
19		533.3
20		557.3
21		617.3
22		562.7
23		579.3

Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
24		559.4
25		615.3
26		503.4
27		563.4
28		596.3
29		555.3
30		473.4
31		475.4
32		599.3

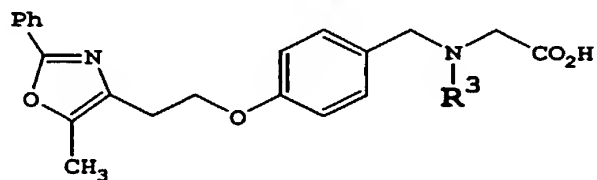
Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
33		517.4
34		507.1
35		507.1
36		496.1
37		557.1
38		591.2
39		568.2
40		625.2
41		591.2
42		568.2
43		622.3

Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
44		601.2
45		557.2
46		519.2
47		675.2
48		519.2
4		600.3
50		564.2
51		545.3
52		625.2
53		563.3

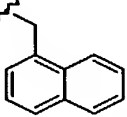
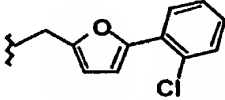
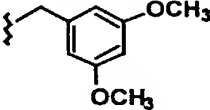
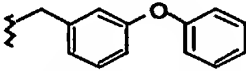
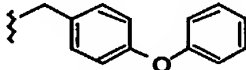
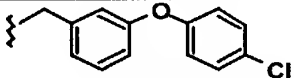
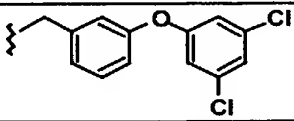
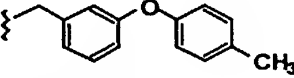
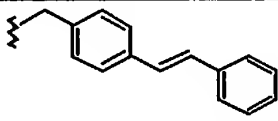
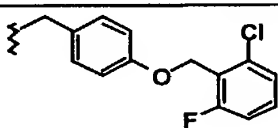
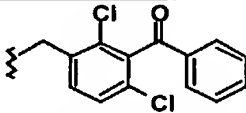
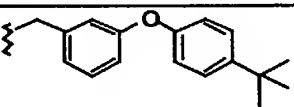
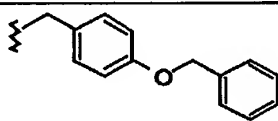


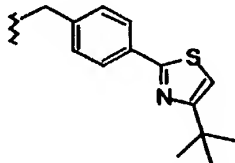
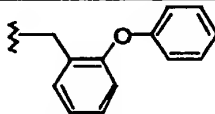
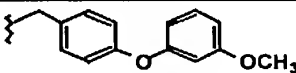
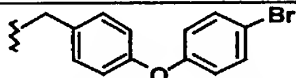
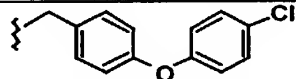
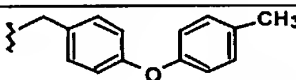
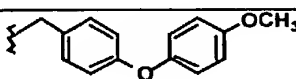
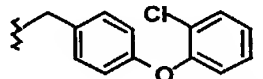
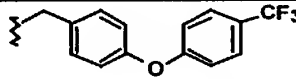
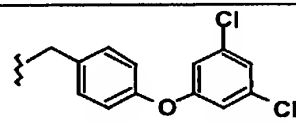
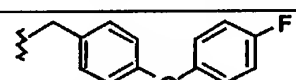
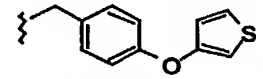
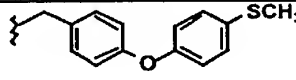
Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
65		537.3
66		537.3
67		636.2

Table 2



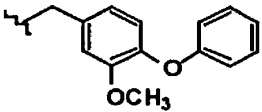
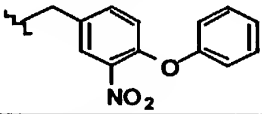
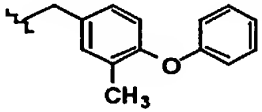
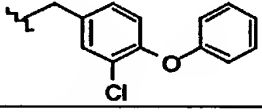
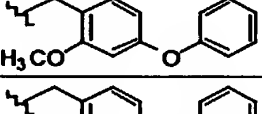
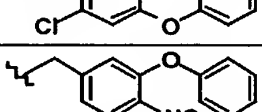
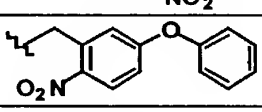
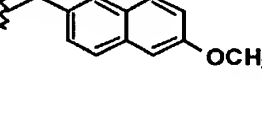
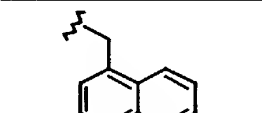
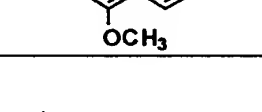
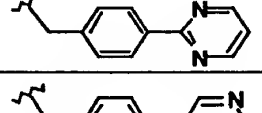
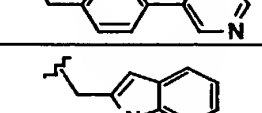
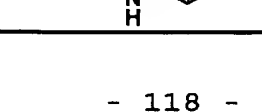
Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
68		534.2
69		547.2
70		465.4
71		533.3
72		473.3

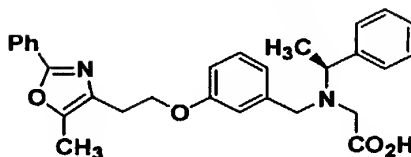
Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
73		507.3
74		587.4
75		517.3
76		549.3
77		549.3
78		583.2
79		617.2
80		563.2
81		559.2
82		615.2
83		629.1
84		605.3
85		563.2

Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
86		596.2
87		549.3
88		635.3
89		639.2
90		583.2
91		563.2
92		635.3
93		583.2
94		617.2
95		617.1
96		567.2
97		555.1
98		595.3

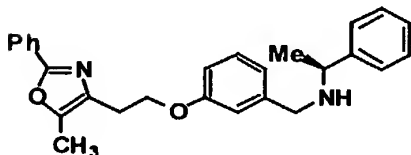




Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
112		579.3
113		594.4
114		563.3
115		583.2
116		579.3
117		583.2
118		594.3
119		594.3
120		537.3
121		537.3
122		535.2
123		535.2
124		496.1

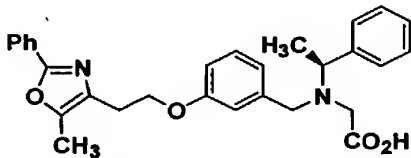
Example 125

5           A.



A solution of Example 7 Part A aldehyde (60 mg; 0.20  
10 mmol) and (S)- $\alpha$ -methyl benzylamine (30 mg; 0.24 mmol) in  
MeOH (1 mL) was stirred at RT for 6 h. The solution was  
cooled to 0°C and a pre-formed solution of NaBH<sub>4</sub> (9 mg;  
0.24 mmol) in MeOH (0.5 mL) was added portionwise. The  
reaction was stirred at RT overnight, then concentrated  
15 in *vacuo* without heating. The residue was partitioned  
between aqueous NaHCO<sub>3</sub> and EtOAc (5 mL each). The  
aqueous layer was extracted with EtOAc (2 x 5 mL). The  
combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and  
concentrated in *vacuo* to give title compound as an orange  
20 yellow-oil (81 mg crude).

B.



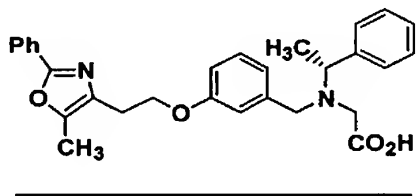
25

A solution of the Part A compound (70 mg; 0.17  
mmol), tert-butyl bromoacetate (66 mg; 0.34 mmol), and  
iPr<sub>2</sub>NEt in DMF (0.5 mL) was stirred at RT for 2 days.  
LC/MS showed that the reaction was complete and clean.

The crude reaction mixture was partitioned between H<sub>2</sub>O (30 mL) and EtOAc (20 mL). The aqueous layer was extracted with Et<sub>2</sub>O (2 x 10 mL); the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the crude amino-tert-butyl ester.

This crude product was stirred in a 1:1 solution of CHCl<sub>3</sub> and TFA (2 mL) for 18 h at RT. The solution was then concentrated *in vacuo* and purified by preparative reverse-phase HPLC (as in Example 10). The purified material was lyophilized from MeOH-H<sub>2</sub>O to give the title compound (71 mg; 71%) as a white lyophilate. [M + H]<sup>+</sup> = 471.2

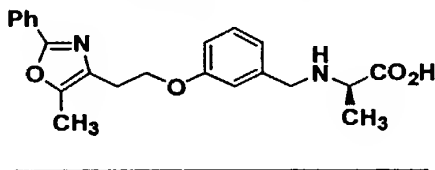
#### Example 126



15

The title compound was synthesized following the same procedure as described above in Example 125 except that (S)- $\alpha$ -methyl benzylamine was replaced by (R)- $\alpha$ -methyl benzylamine in the synthesis of the part A compound. The title compound was obtained in 67% yield (66 mg) overall. [M + H]<sup>+</sup> = 471.2

#### Example 127



25

A mixture of Example 7 Part A compound (30 mg, 0.098 mmol), D-alanine tert-butyl ester hydrochloride (23 mg; 0.127 mmol), Et<sub>3</sub>N (5 drops) and 4A molecular sieves



15

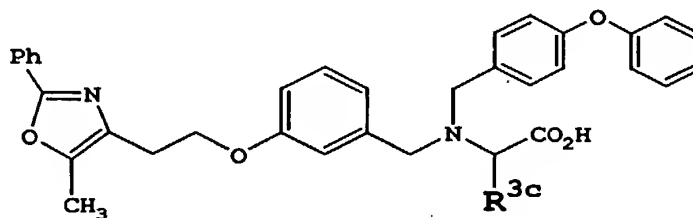
CC1=C(COCc2ccc(cc2)OCCN(Cc3ccccc3)Cc4ccc(Oc5ccccc5)cc4)OC(=N1)c6ccccc6

30

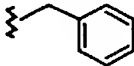
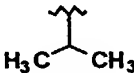
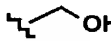
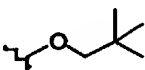
30

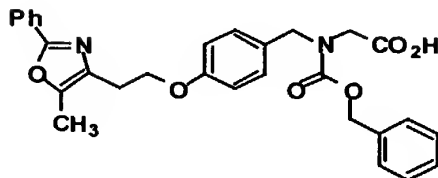
Examples 131 to 135

Other analogs in this series were prepared by analogous procedures and are shown in the following table:

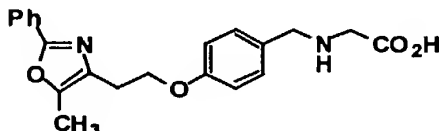


5

Example No.	R <sup>3c</sup>	[M+H] <sup>+</sup>
131	(S)-CH <sub>3</sub>	563.2
132	 (S)	639.3
133	 (R)	591.4
134	 (R)	579.3
135	 (R)	635.4

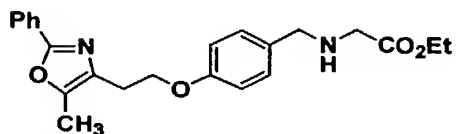
Example 136

A.



5

A solution of the secondary amine ethyl ester (72 mg; 0.183 mmol)

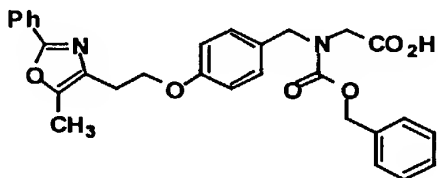


10

(prepared as described in Example 3 Part A) in MeOH (2 mL) and aqueous NaOH (2 mL of a 1M solution) was heated under reflux for 12 h. The pH of the solution was adjusted to 5 (with aqueous 1M NaOH and 1M HCl), upon which a colorless solid precipitated. This was filtered off and the filtrate was extracted with EtOAc (3x); the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give the crude title amino acid as a colorless solid (97 mg).

20

B.



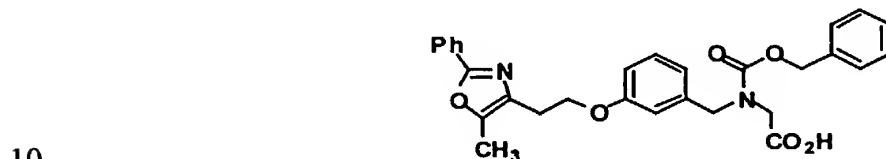
To a solution of the Part A amino acid (15 mg; 0.04 mmol) in dioxane:H<sub>2</sub>O (1:1, 8 mL) was added K<sub>2</sub>CO<sub>3</sub> (22 mg;

25

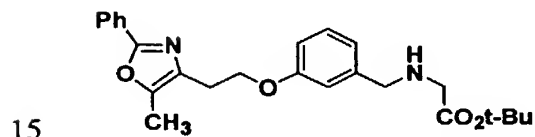


0.16 mmol) followed by benzyl chloroformate (15 mg; 0.09 mmol). The reaction was stirred overnight, then concentrated *in vacuo* and acidified with excess aqueous 1M HCl. This was extracted with EtOAc (3x); the combined  
5 organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo* to give title compound (13 mg; 63%) as a colorless solid. [M + H]<sup>+</sup> = 501.3

Example 137



To a 0°C solution of the amino-tert-butyl ester (75 mg; 0.18 mmol)



(prepared as described in Example 7 Part B), in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added CbzCl (28 µL; 0.20 mmol), followed by Et<sub>3</sub>N (54 µL; 0.39 mmol). The reaction was allowed to warm to RT and then stirred at RT overnight  
20 for 18 h. Aqueous NaHCO<sub>3</sub> (2 mL of a 10% solution) was added and the aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The crude carbamate-ester was dissolved in CHCl<sub>3</sub> (3 mL) and TFA (1 mL); the solution  
25 was stirred at RT for 24 h, then concentrated *in vacuo*. The crude carbamate-acid was purified by reverse-phase preparative HPLC on a C-18 column (continuous gradient over 14 min; 4 min hold time; flow rate = 20 mL/min from 1:1 A:B to 100% B; solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA;  
30 solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA). The product was

5

COC1=CC=C(OC(=O)CN(C1)Cc2ccc(OCCc3c(C)c(Ph)oc3)cc2)C=C1

A solution of 2-methoxyphenol (2 g, 16.1 mmol), N,N-dimethylaniline (1.95 g, 16.1 mmol), phosgene (8.34 mL of a 1.93 M solution in toluene, 16.1 mmol) and a catalytic amount of DMF in chlorobenzene (5 mL) was stirred in a pressure tube for 2 h at 80°C. The organic layer was separated and concentrated in vacuo. The residue was distilled (Buchi Kugelrohr; bp = 115°C @ 10 mm Hg) to provide 2-methoxyphenyl chloroformate (1.5g; 50%) as a clear oil.

COC1=CC=C(OC(=O)CN(C1)Cc2ccc(OCCc3c(C)oc(c3)Ph)cc2)C=C1

25

CCOC(=O)CNCCc1ccc(OCCc2c(C)c(oc2=Nc3ccccc3)cc1)cc1

(prepared as described in Example 7 Part B),  
2-methoxyphenyl chloroformate (8 mg, 0.05 mmol; prepared  
as above) and polyvinylpyridine (Aldrich; 16 mg, 0.3  
mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was stirred for 30 min at RT.

5 Amine resin WA21J (Supelco; 200 mg) was added and the  
mixture was stirred at RT for 30 min in order to remove  
unreacted chloroformate. The reaction mixture was  
filtered and concentrated in vacuo to give the desired 2-  
methoxyphenyl carbamate-ester.

10 The ester was treated with a solution of 30% TFA in  
 $\text{CH}_2\text{Cl}_2$  (5 mL) overnight. Volatiles were removed in vacuo  
to give the crude acid. This material was purified via  
solid-phase extraction using an anion exchange column  
(CHQAX13M6 column; United Technologies; 3 g of sorbent in  
15 a 6 mL column) by the exemplary procedure outlined below.

1) The column was conditioned with MeOH (10 mL) and  $\text{CH}_2\text{Cl}_2$   
(10 mL).

20 2) The crude acid was dissolved in a minimal volume of  
 $\text{CH}_2\text{Cl}_2$  and loaded onto the SAX column.

3) The cartridge was washed with  $\text{CH}_2\text{Cl}_2$  (10 mL),  
 $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (10 mL of a 4:1  $\text{CH}_2\text{Cl}_2:\text{MeOH}$  solution).

25 4) The product was eluted with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (10 mL of a 4:1  
 $\text{CH}_2\text{Cl}_2:\text{MeOH}$  solution).

The product-containing fractions were concentrated  
30 in vacuo on a Speed Vac to afford title compound as an  
oil. Analytical reverse-phase HPLC (standard conditions)  
indicated that the purity of the product was 90%. In  
addition LC/MS gave the correct molecular ion  $[(\text{M}+\text{H})^+ =$   
517.3] for the desired title compound.

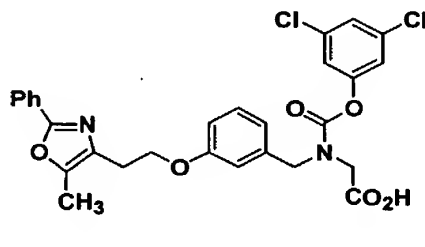
35

CC1=C(C(=N1C2=CC=CC=C2)OCCOC3=CC=C(C=C3)CN(CCC(=O)O)C(=O)Oc4ccc(Cl)cc4)CCCOC(=O)CN(Cc1ccc(OCCc2c(C)c(oc2=N)c3ccccc3)cc1)C(=O)Cl

5

CCOC(=O)CNCCc1ccc(OCCc2c(C)c(Oc3ccccc3)n2)cc1

B.



20

- 128 -

A mixture of the Part A carbamoyl chloride (20 mg; 0.045 mmol), 3,5-dichlorophenol (16 mg; 0.07 mmol), and pyridine (0.5 ml) was stirred at 80°C for 16 h. Pyridine was removed in vacuo and the residue was purified via  
5 solid-phase extraction using a CHQAX1 cartridge (2 g of sorbent in a 6 ml column, 0.3 mg/g) by the procedure outlined below:

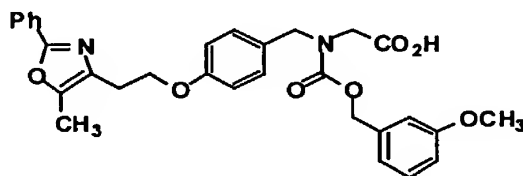
- 1) The column was conditioned with MeOH (10 mL) and  
10 CH<sub>2</sub>Cl<sub>2</sub> (20 mL)
- 2) The reaction mixture in CH<sub>2</sub>Cl<sub>2</sub> was loaded onto the SAX column
- 15 3) The product was eluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL)

The product-containing fractions were concentrated in vacuo using a Speed Vac over 16 h to afford the pure aryl carbamate-tert-butyl ester which was treated with a  
20 solution of 30% TFA in CH<sub>2</sub>Cl<sub>2</sub> overnight. Volatiles were removed using a Speed Vac for 16 h to afford the crude acid final product. The product was initially purified via solid-phase extraction using a Varian SAX cartridge (2 g of sorbent in a 6 mL column, 0.3 meq/g) by the  
25 procedure outlined below:

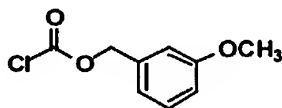
- 1) The column was conditioned with MeOH (10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL)
- 30 2) The reaction mixture in CH<sub>2</sub>Cl<sub>2</sub> was loaded onto the SAX column
- 3) The column was rinsed with CH<sub>2</sub>Cl<sub>2</sub> (10 mL)
- 35 4) The column was rinsed with 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> (10 mL)

The product-containing fractions were concentrated *in vacuo* using a Speed Vac for 16 h to afford the purified product (20 mg, 80%) as a solid. Reverse phase HPLC analysis (YMC S5 ODS 4.6 x 33 mm column, continuous gradient from 50% A to 100% B for 2 min at a flow rate of 5 mL/min [Solvent A = 10%MeOH/90%H<sub>2</sub>O/0.2% H<sub>3</sub>PO<sub>4</sub>; Solvent B = 90%MeOH/10% H<sub>2</sub>O/0.2% H<sub>3</sub>PO<sub>4</sub>]) indicated that the product purity was 96%. In addition, LC/MS gave the correct molecular ion [(M+H)<sup>+</sup> = 555.2] (electrospray) for the title compound.

## 15



A.



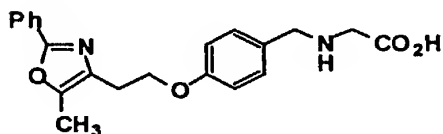
- 130 -

5

COC1=CC=C(C=C1)COCC(=O)N(Cc2ccc(OCC3=C(C)N(=C3C4=CC=CC=C4C5=CC=CC=C5C=C6C(=O)O)C6)Cc3ccc(OCC4=C(C)N(=C4C5=CC=CC=C5C=C6C(=O)O)C6)cc3

The title compound was prepared as part of a solution phase library which was run using the following standard procedure.

15



20

25

- 1) The column was conditioned with MeOH (10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (10 mL)

3) The cartridge was washed successively with  $\text{CH}_2\text{Cl}_2$  (10 mL), 20%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  (10 mL).

4) The product was eluted with a solution of 20%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  (10 mL).

15  $[(M+H)^+ = 531.3]$  for the desired title compound.

### Example 141



A.



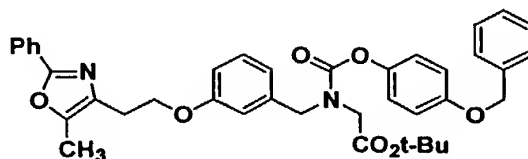
30 was allowed to cool to RT. The upper clear solution was



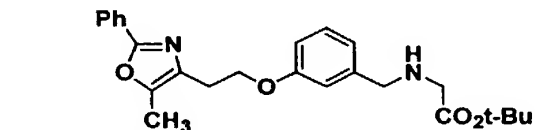
separated and concentrated *in vacuo* to give the crude title aryl chloroformate as crystals (2 g crude product).

B.

5



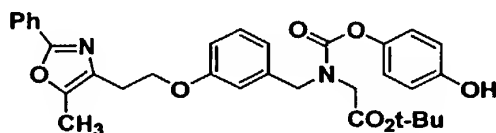
To a mixture of the Part A chloroformate (184 mg, 0.70 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) and polyvinylpyridine (Aldrich; 315 mg, 1 mmol) was added a solution of the amino-tert-butyl ester (280 mg, 0.66 mmol)



(prepared as described in Example 7 Part B), in  $\text{CH}_2\text{Cl}_2$  (5 mL). The reaction was stirred at RT for 15 min. Resin-bound amine (WA21J, Supelco; 150 mg) was added to the mixture. The reaction mixture was stirred for another 15 min. The resin-bound amine and polyvinylpyridine were filtered off and the filtrate was concentrated *in vacuo* to give the crude product. The crude product was chromatographed ( $\text{SiO}_2$ ; hexane/EtOAc 1:4) to provide title compound (0.30 g, 70%).

C.

25

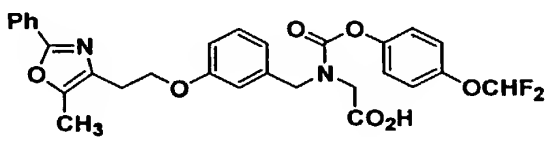


A solution of Part B compound (75 mg; 0.42 mmol) in 20 ml MeOH was hydrogenated in the presence of 20 mg of 10% Pd/C under an atmosphere of  $\text{H}_2$  (balloon) for 24 h.

The palladium catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give the crude title t-butyl ester (240 mg, 90%) which was used without further purification in the next step.

5

D.

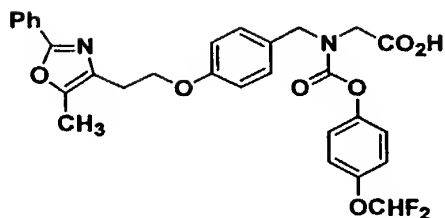


10 The solution of Part C phenol-tert-butyl ester (50 mg; 0.089 mmol), catalytic Bu<sub>4</sub>NBr (1.5 mg, 0.0047 mmol), aq NaOH (0.7 mL of a 1 M solution) and isopropanol (2 mL) in a pressure tube was cooled to -50°C. Freon gas was bubbled into the solution for 1 min. The tube was sealed  
15 and heated to 80°C for 12 h. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give an oil, which was then treated with a solution of 30% TFA in CH<sub>2</sub>Cl<sub>2</sub> overnight. Volatiles were  
20 removed *in vacuo* and the residue was purified using preparative HPLC (YMC S5 ODS 30 x 250mm reverse phase column; 30 minute continuous gradient from 70:30 A:B to 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA, and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to afford the desired title  
25 product (14 mg; 28%). Reverse Phase HPLC analysis indicated that the product purity was 97%. In addition LC/MS (electrospray) gave the correct molecular ion [(M+H)<sup>+</sup> = 553.1] for the desired compound.

30

#### Example 142

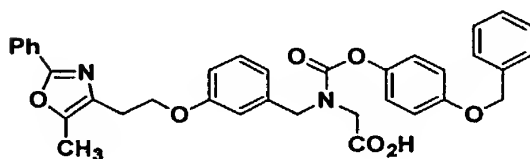
Following the Example 141 procedure, the analogous compound was prepared [(M+H)<sup>+</sup> = 553.2]:



Intermediates corresponding to Example 141 Parts B and C were deprotected using the same TFA/ $\text{CHCl}_3$  procedure as above and purified as usual to give the following

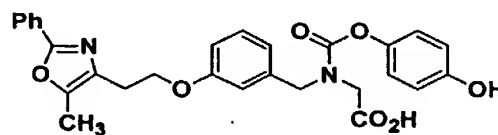
5 analogs:

Example 143



Example 143:  $[M + H]^+ = 593.4$

Example 144

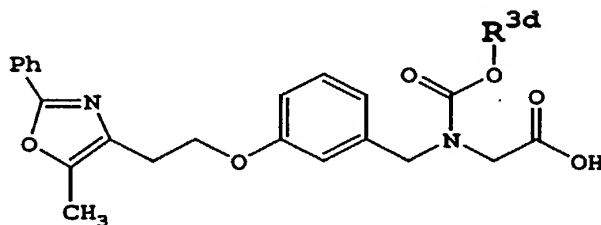


10 Example 144:  $[M + H]^+ = 503.1$

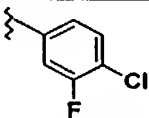
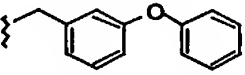
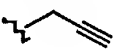
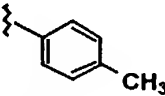
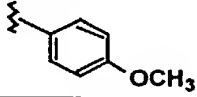
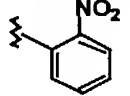
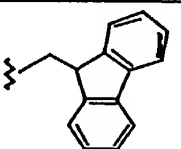
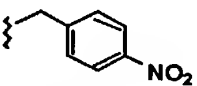
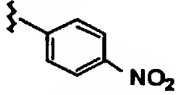
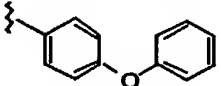
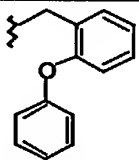
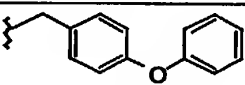
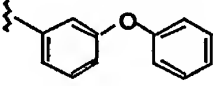
Examples 145 to 305

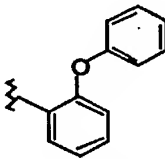
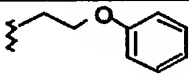
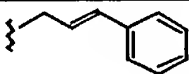
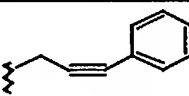
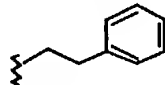
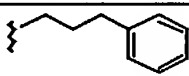
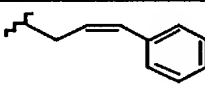
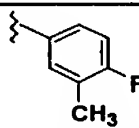
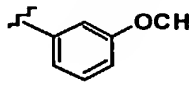
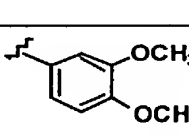
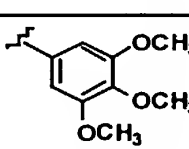
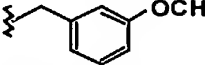
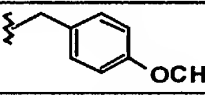
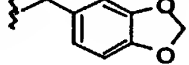
The following carbamate-acid analogs in Tables 4 and  
15 5 were synthesized according to one of the above methods:

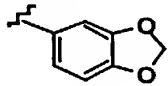
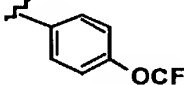
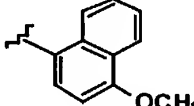
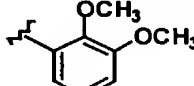
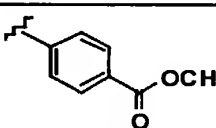
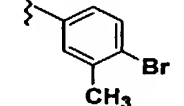
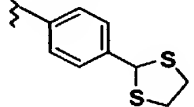
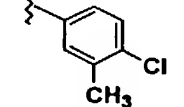
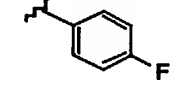
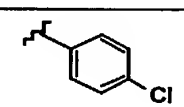
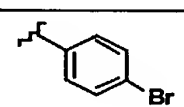
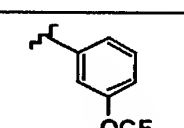
**Table 4**



Example No.	$R^{3d}$	$[M+H]^+$
145		487.2

Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
146		539.3
147		593.2
148		449.3
149		501.3
150		517.2
151		532.2
152		589.3
153		546.3
154		532.2
155		579.2
156		593.2
157		593.3
158		579.2

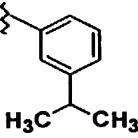
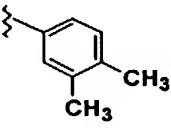
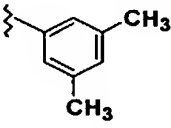
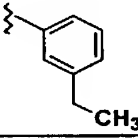
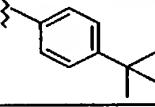
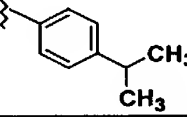
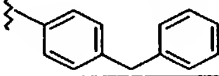
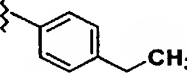
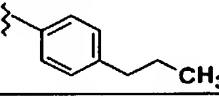
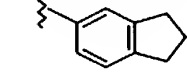
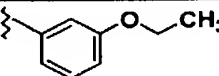
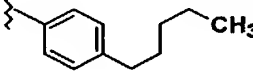
Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
159		579.2
160		531.2
161		527.2
162		525.2
163		515.2
164		529.2
165		527.2
166		519.3
167		517.3
168		547.3
169		577.3
170		531.3
171		531.3
172		545.3

Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
173		531.3
174		571.2
175		567.3
176		547.3
177		545.3
178		579.2
179		591.2
180		535.2
181		505.2
182		521.1
183		566 + 588
184		571.1



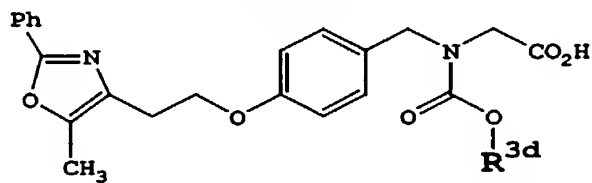




Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
206		529.4
207		515.3
208		515.3
209		515.3
210		543.3
211		529.4
212		577.3
213		515.3
214		529.3
215		527.3
216		531.3
217		557.3

Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
218		573.1
219		519.2
220		535.2
221		585.2
222		519.2
223		535.2
224		585.2
225		561.2

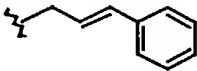
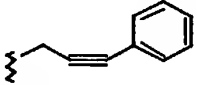
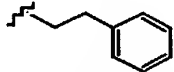
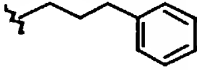
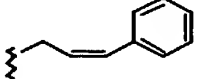
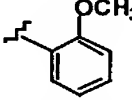
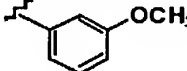
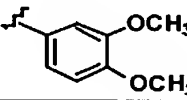
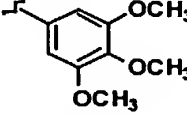
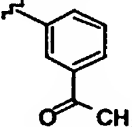
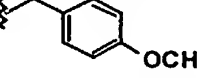
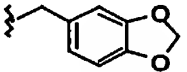
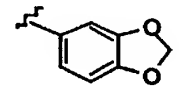
Table 5

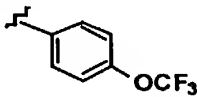
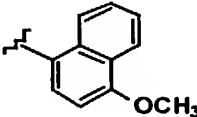
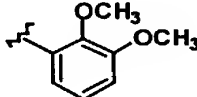
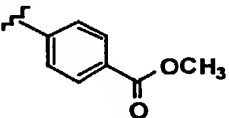
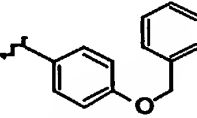
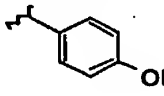
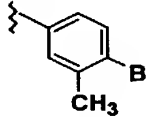
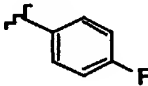
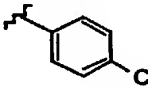
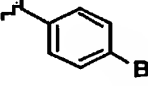


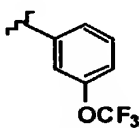
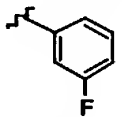
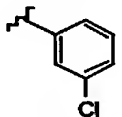
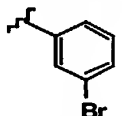
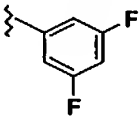
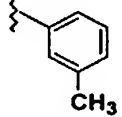
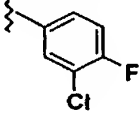
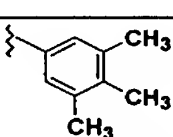
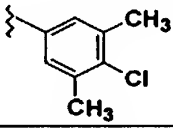
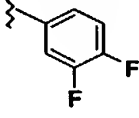
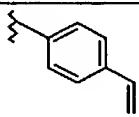
5

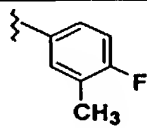
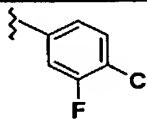
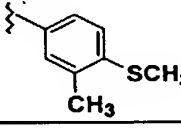
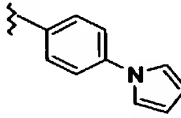
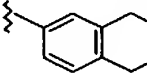
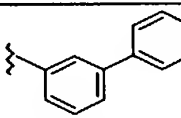
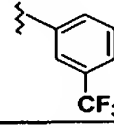
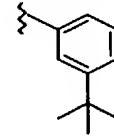
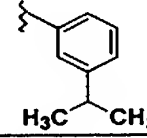
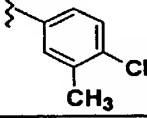
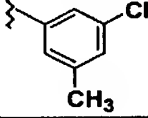
Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
226		545.2

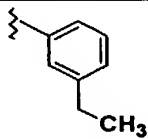
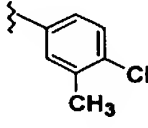
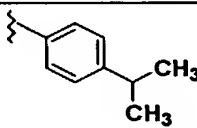
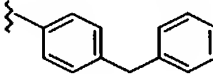
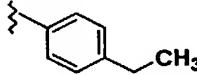
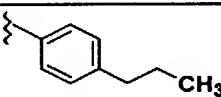
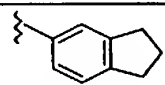
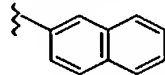
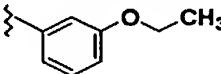
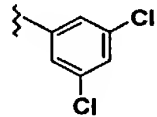
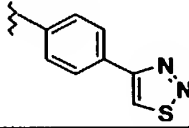
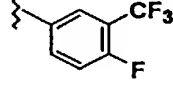
- 143. -

Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
241		527.2
242		525.2
243		515.2
244		529.2
245		527.2
246		517.3
247		517.3
248		547.3
249		577.3
250		543.1
251		531.3
252		545.3
253		531.3

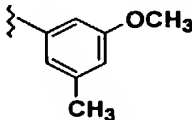
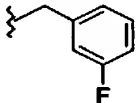
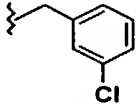
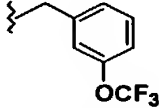
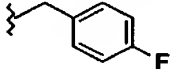
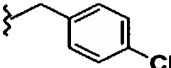
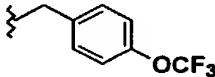
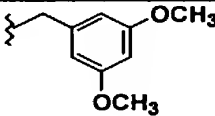
Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
254		571.2
255		567.3
256		547.3
257		545.3
258		593.4
259		503.2
260		579.2
261		505.2
262		521.1
263		566/567

Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
264		571.1
265		505.2
266		521.1
267		566/567.0
268		523.3
269		501.3
270		539.2
271		529.3
272		549.2
273		523.2
274		513.3

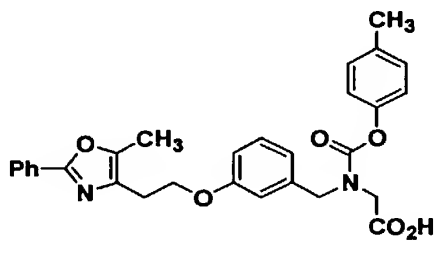
Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
275		519.2
276		539.2
277		547.3
278		552.3
279		541.3
280		563.3
281		555.3
282		543.3
283		529.3
284		515.3
285		515.3

Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
286		515.3
287		535.2
288		529.2
289		577.3
290		515.2
291		529.2
292		527.3
293		537.3
294		531.3
295		555.2
296		571.3
297		573.2



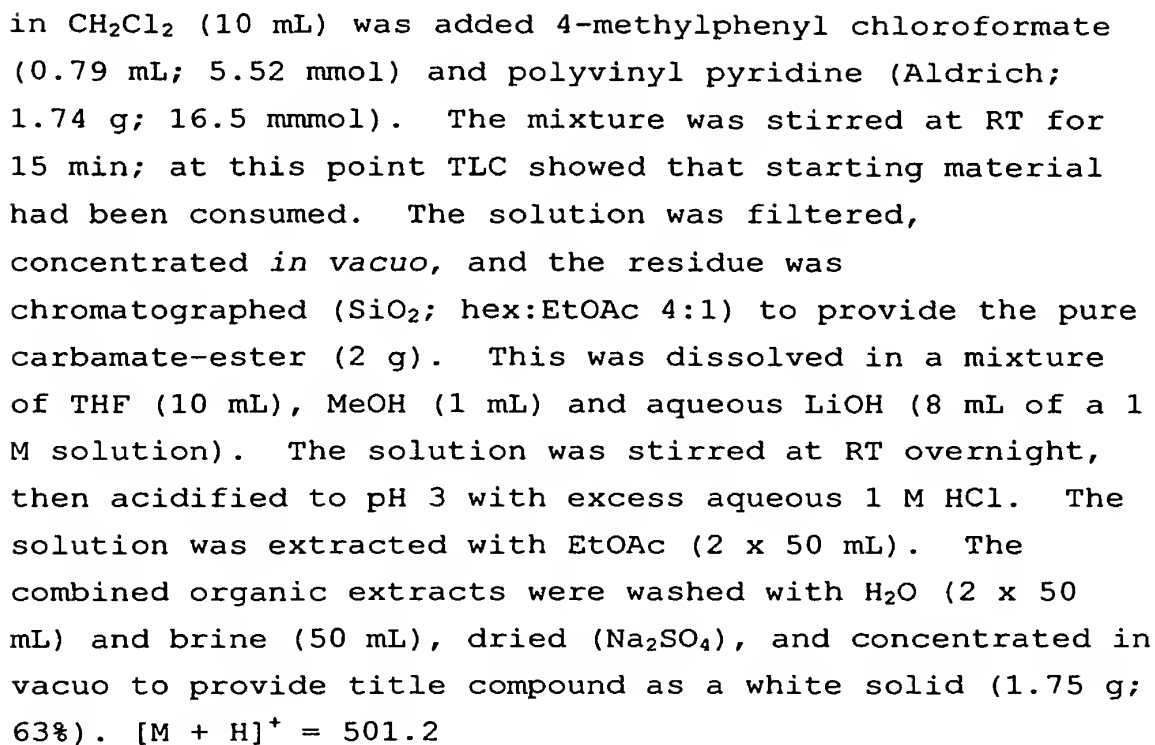
Example No.	R <sup>3d</sup>	[M+H] <sup>+</sup>
298		531.3
299		519.3
300		535.2
301		585.2
302		519.2
303		535.2
304		585.2
305		561.2

### Example 149



5

To a solution of the secondary amine-ester (2.1 g;  
5.52 mmol)

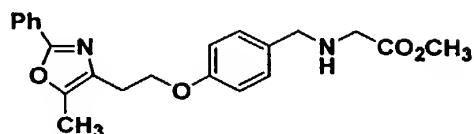


[M + H]<sup>+</sup> = 501.2; <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 7.93-7.99 (m, 2H), 7.38-7.43 (m, 3H), 7.23 (q, 1H, J = 8 Hz), 7.02-7.12 (m, 3H), 6.98-7.02 (m, 2H), 6.82-6.89 (m, 2H), 4.71 (s, 1H), 4.64 (s, 1H), 4.25 (t, 2H, J = 7 Hz), 4.07 (s, 2H), 2.90-2.98 (m, 2H), 2.37 (s, 3H), 2.29 (s, 3H)

### Example 230



To a 0°C solution of the secondary amine (3.0 g; 7.9 mmol)



in CH<sub>2</sub>Cl<sub>2</sub> (45 mL) were successively added pyridine (0.8 mL; 9.9 mmol) and 4-methoxyphenyl chloroformate (1.3 mL; 8.7 mmol). The reaction was stirred at 0°C for 3 h, at which point starting material had been consumed (by analytical HPLC). The reaction solution was washed with aqueous HCl (2 x 25 mL of a 1 M solution), brine (2x), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo*. The crude product was chromatographed (SiO<sub>2</sub>; stepwise gradient from 4:1 to 3:7 hex:EtOAc) to provide the desired carbamate-ester (4.2 g; 100%). The ester was dissolved in THF:MeOH:H<sub>2</sub>O (50 mL of a 3:1:1 solution) and LiOH.H<sub>2</sub>O (0.5 g; 11.9 mmol) was added. The solution was stirred overnight at RT. Starting material was still present by HPLC. More LiOH.H<sub>2</sub>O (0.2 g; 4.8 mmol) was added and the mixture was briefly heated to solubilize the LiOH, then stirred at RT for 4 h. The reaction was complete at this point, and the mixture was acidified to pH 3 with excess aqueous 1 M HCl, then organic solvents were removed in *vacuo*. The residual aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic extracts were successively washed with H<sub>2</sub>O and brine (50 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give title compound as a colorless solid (3.07 g; 75%).

[M + H]<sup>+</sup> = 517.2; <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>): δ 7.96–7.98 (m, 2H), 7.4–7.45 (m, 3H), 7.2–7.3 (m, 2H), 7.0–7.1 (m, 2H), 6.8–7.0 (m, 4 H), 4.65 (s, 1H), 4.55 (s, 1H), 4.20–4.24 (m, 2H), 4.02 (s, 2H), 3.77 (s, 3H), 3.00 (s, 2H), 2.38 (s, 3H).

5

COc1ccc(cc1)OC(=O)NCCN(Cc2ccc(OCCc3c(C)c(oc3c4ccccc4)cc5ccccc52)cc6ccccc6)C(=O)O

15

CC1=C(Cc2ccc(OCCN(Cc3ccc(OCC4=CC=CC=C4C5=CC=CC=C5)C6=CC=CC=C6)C(=O)O)C=C3C=C1C2=CC=CC=C2)C(=O)OC3=CC=C(C=C3)Br

25

CC1=C(C(=O)NCC(=O)O)C(=O)Oc2ccc(OCCc3c(C)c(oc3-c4ccccc4)cc5c(C)cc(C)cc5)cc2

5

## 10



15

## 20



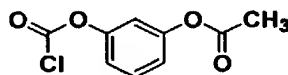
25

CC1=C(C2=CC=CC=C2)N=C(C3=CC=CC=C3)O1CCOC4=CC=CC=C4CN(C)C(=O)Oc5ccc(Br)cc5

10 Hz, 2H)

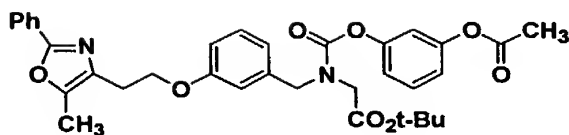
COc1cc(OC(=O)CN(Cc2ccc(OCCc3c(C)c(OC4=CC=CC=C4C5=CC=CC=C5)N3)c2)C(=O)Oc6ccc(OCCF)cc6)cc1

A.

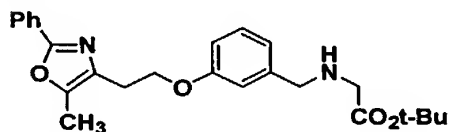


30

B.



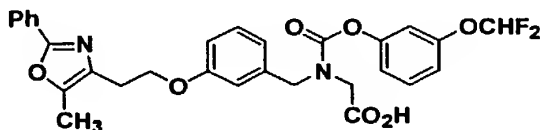
- 5 To a mixture of Part A chloroformate (50 mg, 0.237 mmol) and polyvinylpyridine (PVP) (75 mg, 0.70 mmol) was added a  $\text{CH}_2\text{Cl}_2$  solution (2 mL) of the amino-tert-butyl ester (100 mg, 0.237 mmol),



- 10 (prepared as described in Example 7 Part B).

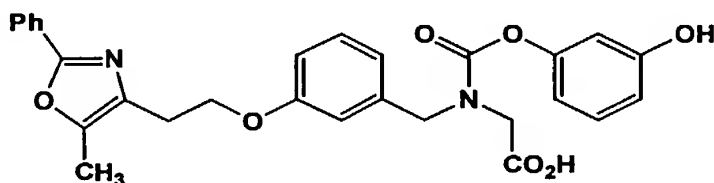
The reaction was stirred at RT for 15 min. Resin-bound amine (WA21J, Supelco; 150 mg) was added to the mixture. The reaction mixture was stirred for another 15 min. The Resin-bound amine and PVP were removed via  
 15 filtration and the filtrate was concentrated *in vacuo* to give the crude product. The crude product was chromatographed ( $\text{SiO}_2$ ; hexane/EtOAc 1:4) to provide title compound (0.1 g, 70%).

20 C.



- 25 A solution of the Part B phenol-tert butyl ester compound (60 mg; 0.10 mmol),  $\text{Bu}_4\text{NBr}$  (0.32 mg, 0.001 mmol), aqueous NaOH (0.5 mL of a 1 M solution; 0.5 mmol) and isopropanol (1 mL) in a pressure tube was cooled to  $-50^\circ\text{C}$ . Freon gas was bubbled into the solution for 1 min. The tube was sealed and heated to  $80^\circ\text{C}$  for 12 h.

The mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to give the crude difluoromethoxy ether-tert butyl ester as an oil. The crude ester was then treated with a solution of 30% TFA in  $\text{CH}_2\text{Cl}_2$  overnight. Volatiles were removed *in vacuo* and the residue was purified using preparative reverse-phase HPLC (as in Example 127, except that the continuous gradient used was from A:B 70:30 to 100% B) to afford two products, the desired title difluoromethoxy ether-acid (13 mg; 23%) and the phenol-acid set out below (32 mg; 63%). Reverse phase HPLC analysis using standard conditions indicated that the product purity was >92%. In addition LC/MS (electrospray) gave the correct molecular ion  $[(M+H)^+ = 553.2 \text{ and } 503.2 \text{ respectively}]$  for the two compounds.

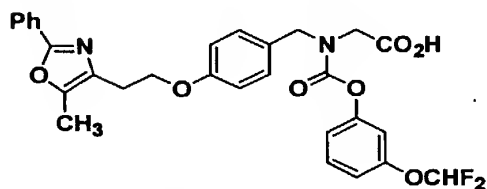


**Phenol-Acid**

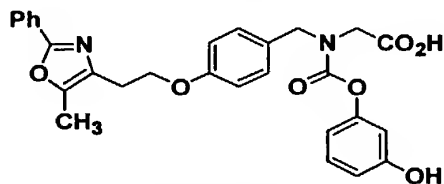
20

Examples 307 and 308

Following the above general procedure of Example 306, the following compounds were prepared:



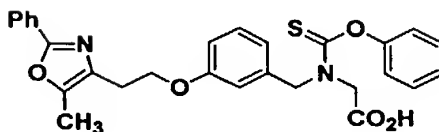
**Example 307**



**Example 308**

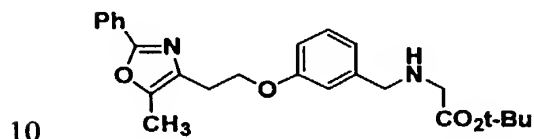
25 Example 307:  $[M + H]^+ = 553.2$ Example 308:  $[M + H]^+ = 503.2$



Example 309

5

To a mixture of phenyl chlorothionoformate (11 mg, 0.063 mmol) and triethylamine (6.5 mg, 0.063 mmol) was added a solution of the amino-tert-butyl ester (20 mg, 0.053 mmol),



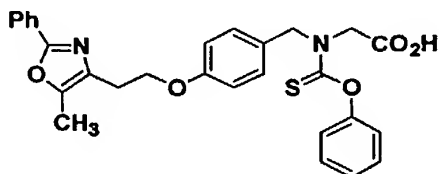
(prepared as described in Example 7 Part B) in  $\text{CH}_2\text{Cl}_2$  (1 mL). The reaction was stirred at RT for 15 min and the mixture was concentrated *in vacuo* to give the crude thionocarbamate tert-butyl ester. This material was dissolved in aqueous LiOH (0.50 mL of a 1.0 M solution) and THF (2 mL) and stirred at RT for 5 h. The solution was concentrated *in vacuo* to give the crude acid as an oil. The crude product was purified using preparative HPLC to afford the desired title product (10 mg; 38%).  $[\text{M} + \text{H}]^+ = 503.2$

20

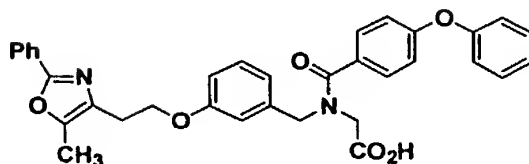
Example 310

The corresponding thiocarbamate in the 1,4 series was prepared in the same manner as described for Example 309.

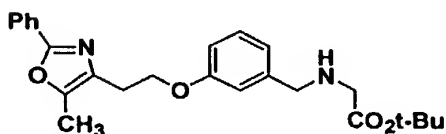
25



$[\text{M} + \text{H}]^+ = 503.2$

Example 311

5 To a mixture of the amine-tert butyl ester (306 mg, 0.73 mmol)

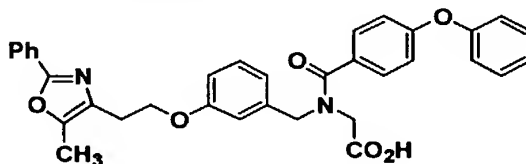


(prepared as described in Example 7 Part B),  
and p-phenoxybenzoic acid (220 mg; 1.02 mmol; 1.4 equiv)  
10 in CH<sub>3</sub>CN (20 mL) was added BOP reagent (372 mg, 0.84 mmol, 1.15 equiv) in a single portion followed by iPr<sub>2</sub>NEt (0.5 mL; 2.9 mmol; 3.9 equiv) dropwise. The reaction was stirred overnight at RT, after which volatiles were removed *in vacuo*. The residue was dissolved in EtOAc and  
15 washed with aqueous 1N HCl. The aqueous layer was extracted with EtOAc (2x) and the combined organic extracts were washed with H<sub>2</sub>O, sat'd aqueous NaHCO<sub>3</sub> and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give the desired product. The resulting crude amide-ester was  
20 used in the next step without further purification.

A solution of the crude amide ester in 40% TFA-CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was stirred for 5h at RT. Volatiles were removed *in vacuo* and the crude acid was purified by Prep HPLC (YMC S5 ODS 30mm x 250 mm reverse phase column; flow rate  
25 = 25 mL/min; 30 min continuous gradient from 70:30 A:B to 100% B; solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to yield title compound (238 mg; 58% yield over 2 steps) as a white solid. Analytical Reverse-phase HPLC: Retention time = 7.53 min.  
30 (Continuous gradient solvent system: from 50% A:50% B to

0% A:100% B (A = 90% H<sub>2</sub>O/10% MeOH/0.2% H<sub>3</sub>PO<sub>4</sub>; B = 90% MeOH/10% H<sub>2</sub>O/0.2% H<sub>3</sub>PO<sub>4</sub>) for 8 min; detection at 220 nm; YMC S3 ODS 4.6 x 50 mm column). [M + H]<sup>+</sup> = 563.3

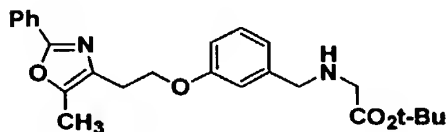
5

Example 311A

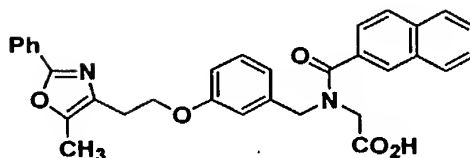
(alternative synthetic procedure)

10

To a solution of the secondary amine tert-butyl ester (35 mg, 0.083 mmol), (prepared as described in Example 7 Part B)

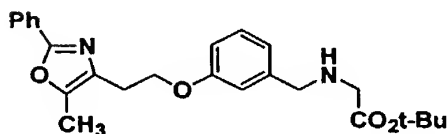


- 15 4-phenoxy benzoic acid (30 mg, 0.14 mmol) and HOAT (30 mg, 0.22 mmol) in THF/DMF (1 mL/0.05 mL) was added EDCI (20 mg, 0.10 mmol) and the mixture was stirred at RT overnight. The reaction was diluted with EtOAc, washed with aqueous 1N HCl, H<sub>2</sub>O, sat'd. aqueous NaHCO<sub>3</sub> and
- 20 brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The crude amide-tert butyl ester was dissolved in TFA/CH<sub>2</sub>Cl<sub>2</sub> (5 mL of a 1:1 solution). The resulting pink solution was stirred overnight and concentrated in vacuo to provide the crude acid-amide as a dark brown oil. The
- 25 crude product was purified by preparative HPLC (YMC S5 ODS 20 x 100 mm column, 10 min continuous gradient from 60:40 A:B to 100 % B; solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA; flow rate = 20 mL/min) to provide the title compound (32 mg, 69%).
- 30 [M + H]<sup>+</sup> = 563.3

Example 312

5

- 1) To a solution of the secondary amine-tert-butyl ester  
(25 mg; 0.06 mmol)



- (prepared as described in Example 7 Part B),  
10 in THF (0.5 mL) was added 2-naphthalene carboxylic acid  
(25 mg; 0.15 mmol; 2.5 equiv).

2) HOAT (48 mg; 0.35 mmol; 5.8 equiv) was added.

15 3) DMF (50  $\mu$ L) was added.

4) EDCI ((20 mg, 0.1 mmol, 1.8 m eq) was added.

5) The reaction vessel was shaken for 24 h at RT.

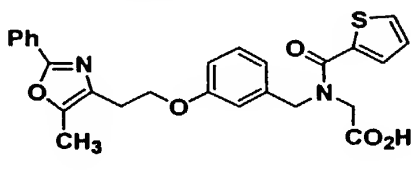
20

6) The reaction was diluted with MeOH (2 mL) and  
filtered.

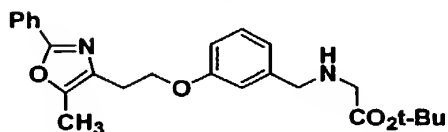
7) The amide-tert butyl ester was purified by preparative  
25 HPLC (YMC S5 ODS 20 x 100 mm column; flow rate = 25  
mL/min; 10 min continuous gradient from 70:30 A:B to  
100% B; solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA; solvent B =  
90:10:0.1 MeOH:H<sub>2</sub>O:TFA).

8) The fractions containing the purified amide-ester were treated with a solution of TFA in  $\text{CH}_2\text{Cl}_2$  (0.5 mL of a 1:1 solution) overnight. The reaction was concentrated in vacuo (Speed Vac) to give title compound (8 mg; 25%). Reverse-phase analytical HPLC showed that the purity of the product was > 88%; LC/MS (electrospray detection) gave the correct  $[\text{M} + \text{H}]^+ = 521.2$  for the title compound.

Example 313



A mixture of the amino-ester (20 mg; 0.0474 mmol),



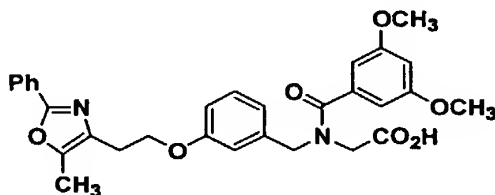
(prepared as described in Example 7 Part B),

thiophene-2-carboxylic acid (9.1 mg, 0.71 mmol), EDCI (26 mg, 1.4 mmol) and DMAP (a catalytic amount) was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) and stirred at RT overnight. The reaction solution was successively washed with aqueous 1N HCl (2 mL) and sat'd aqueous  $\text{NaHCO}_3$  (2 mL). To the organic phase was then added 0.5 g anhydrous  $\text{Na}_2\text{SO}_4$ , and 0.2 g WA21J amine-bound resin (Supelco). The mixture was shaken for 0.5 h and the solids were filtered off. TFA (2.0 mL) was added to the filtrate and the solution was shaken at RT overnight. The reaction solution was concentrated in vacuo using a Speed Vac for 16 h to afford title compound as a yellow oil. Reverse phase analytical HPLC (YMC S5 ODS 4.6 x 33 mm column, continuous gradient from 100% A to 100%B for 2 min at a

flow rate of 5 mL/min [Solvent A = 10% MeOH/90% H<sub>2</sub>O/0.2% H<sub>3</sub>PO<sub>4</sub>; Solvent B = 90% MeOH/10% H<sub>2</sub>O/0.2% H<sub>3</sub>PO<sub>4</sub>]) indicated that the product purity was 92.7%. In addition, LC/MS (electrospray) gave the correct molecular ion [(M+H)<sup>+</sup> = 477.2] for the desired title compound.

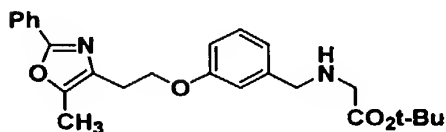
#### Example 314

Another purification protocol using amine-bound resin for the amide-acid product is illustrated by the following synthesis:



15

To a mixture of the amino-ester (20 mg; 0.0474 mmol),



20

(prepared as described in Example 7 Part B), and 3,5-dimethoxybenzoic acid (13 mg, 0.071 mmol) in anhydrous CH<sub>3</sub>CN (0.5 mL) was added a solution of BOP reagent (31 mg, 0.071 mmol) in CH<sub>3</sub>CN (0.5 mL), followed by DIEA (41  $\mu$ L, 0.23 mmol) in CH<sub>3</sub>CN (0.5 mL). The reaction was shaken at RT overnight. Volatiles were removed *in vacuo* using a Speed Vac and CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added. The solution was washed successively with aqueous 1N HCl (2 mL) and sat'd aqueous NaHCO<sub>3</sub> (2 mL). To the organic phase was added 0.5 g anhydrous Na<sub>2</sub>SO<sub>4</sub>, and 0.2 g

30

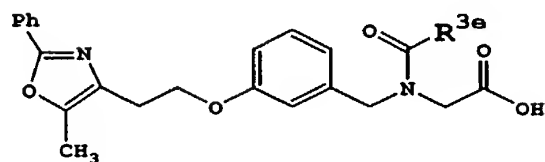
WA21J amine-bound resin (Supelco). The mixture was shaken for 0.5 h and the solids were filtered. TFA (2 mL) was added to the filtrate and the solution was shaken at RT overnight. The reaction solution was concentrated in vacuo using a Speed Vac for 16 h to afford the final product as a yellow gum. Reverse-phase analytical HPLC (YMC S5 ODS 4.6 x 33 mm column, continuous gradient from 100% A to 100% B for 2 min at a flow rate of 5 mL/min [Solvent A = 10% MeOH/90% H<sub>2</sub>O/0.2% H<sub>3</sub>PO<sub>4</sub>; Solvent B = 90% MeOH/10% H<sub>2</sub>O/0.2% H<sub>3</sub>PO<sub>4</sub>]) indicated that the product purity was 90%. In addition, LC/MS (electrospray) gave the correct molecular ion [(M+H)<sup>+</sup> = 531.3] for the title compound.

15

Examples 315 to 391

Following one of the above procedures, the following compounds in Tables 6 and 7 of the invention were prepared.

Table 6: (Amide-Acids)



Example No.	R <sup>3e</sup>	[M+H] <sup>+</sup>
315		521.2
316		507.3
317		563.1
318		561.2
319		499.3
320		559.2
321		491.1
322		522.2
323		491.2
324		543.3



- 165 -

- 166 -

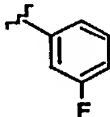
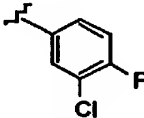
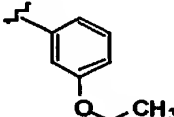
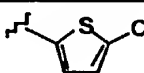
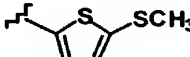
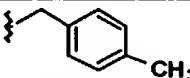
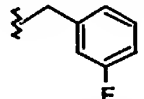
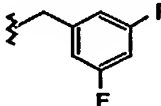
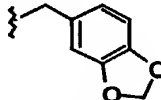
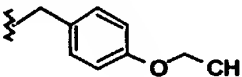
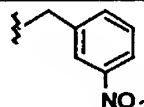
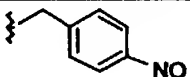
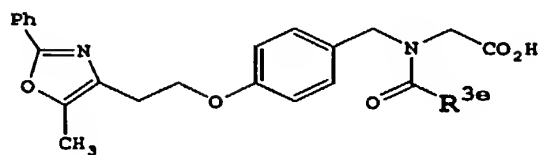
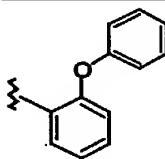
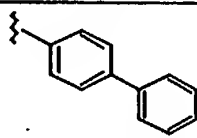
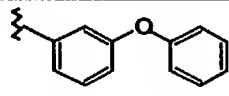
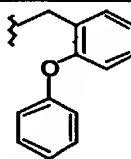
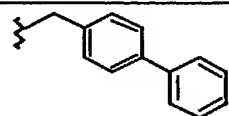
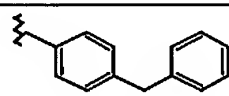
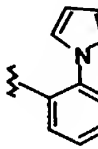
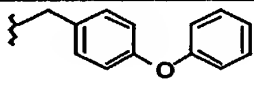
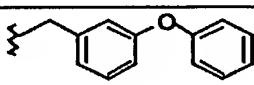
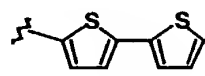
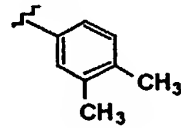
Example No.	R <sup>3e</sup>	[M+H] <sup>+</sup>
350		489.3
351		523.2
352		515.3
353		511.2
354		523.1
355		499.2
356		503.2
357		521.2
358		529.2
359		529.2
360		530.2
361		530.2

Table 7: (Amide-Acids)



Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
362		499.2
363		547.2
364		563.2
365		561.1
366		595.1
367		593.1
368		595.1
369		597.1

Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
370		563.1
371		547.2
372		563.1
373		577.2
374		561.2
375		561.2
376		536.2
377		577.2
378		577.2
379		615.3
380		499.3

- 170 -

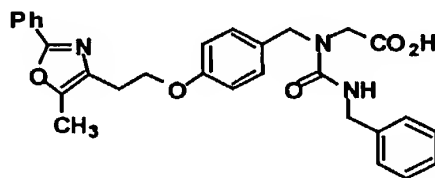
Cc1c(Cc2ccc(OCC3C(=O)N(C3)c4ccccc4)c2)c(=O)oc1Cc5ccc(OCC(=O)Nc6ccccc6)cc5CCOC(=O)N(Cc1ccccc1)C(=O)N(Cc2ccc(OCCc3c(C)c(OC)c(C4=CC=CC=C4C5=CC=CC=C5N=C34)C6=CC=CC=C6)cc2)C7=CC=CC=C7

5

CCOC(=O)NCCNc1ccc(OCCc2c(C)c(oc2=Nc3ccccc3)cc1)cc1

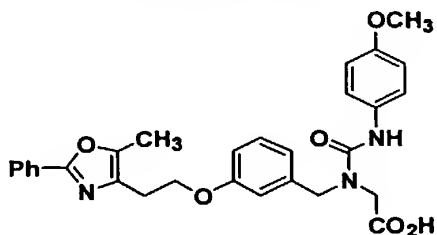
10

B.

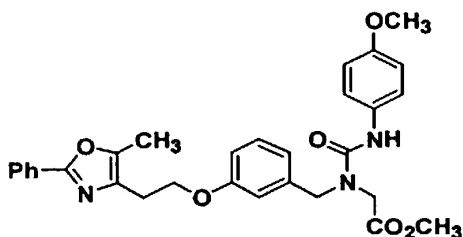


25

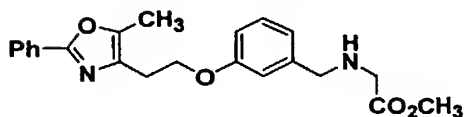
A solution of the crude Part A urea-ethyl ester (53 mg) and LiOH.H<sub>2</sub>O (12 mg) in THF: MeOH:H<sub>2</sub>O (3:1:1; 5 mL) was stirred at RT for 2 days. The solution was acidified to pH3 with aqueous 1M HCl, concentrated *in vacuo*, and purified by preparative HPLC (utilizing a YMC S5 ODS 20mm x 100 mm column; with a continuous gradient from 70%A:30%B to 100% B for 10 minutes at a flow rate of 20 mL/min, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and where B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give title compound (12 mg; 24%) as an off-white solid. [M + H]<sup>+</sup> = 500.2

Example 393

15 A.



To a solution of the amine (0.25 g, 0.66 mmol)

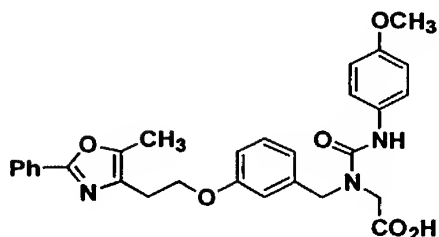


20

(prepared as described in Example 6), in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added 4-methoxyphenyl isocyanate (0.20 g, 1.32 mmol) in one portion and the resulting solution was stirred for 1 h at RT. The reaction mixture was then concentrated *in vacuo* to give an oil, which was



B.



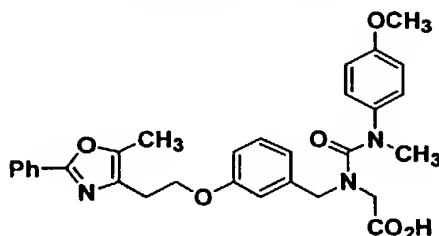
A solution of Part A compound (0.14 g, 0.26 mmol) and LiOH (0.1 g, 4.3 mmol) in H<sub>2</sub>O/THF (5 ml of a 40:60 solution) was stirred for 12 h at 25°C. The reaction mixture was acidified with HOAc and extracted with EtOAc (2x). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo to provide title compound (0.12 g; 90%) as a colorless oil. [M + H]<sup>+</sup> = 516

15

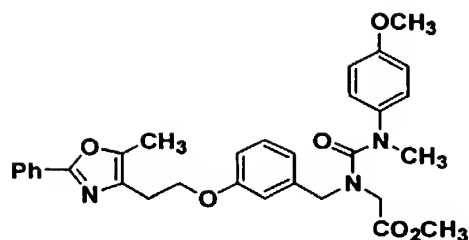
<sup>1</sup>H NMR (CD<sub>3</sub>OD; δ): 7.94 (m, 2H), 7.45 (m, 3H), 7.23 (m, 3H), 6.80 (m, 2H), 6.80 (m, 3H), 4.58 (s, 2H), 4.23 (t, J = 7.9 Hz, 2H), 3.81 (s, 2H), 3.73 (s, 3H), 2.98 (t, J = 7.9 Hz, 2H), 2.36 (s, 3H).

20

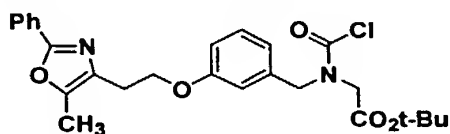
### Example 394



A.

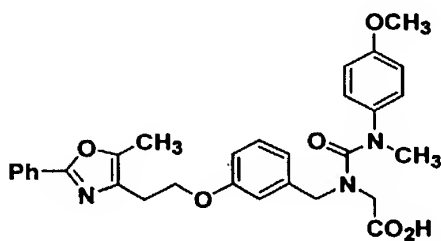


5 A solution of the previously described carbamoyl chloride (Example 139 Part A compound; 0.15 g; 0.34 mmol)



N-methyl-p-anisidine (0.14 g, 1.0 mmol) and  $K_2CO_3$  (0.15 g, 1.1 mmol) in 5 ml of acetone was stirred at 25 °C for 12  
 10 h. The reaction mixture was concentrated in vacuo to yield an oily residue, which was chromatographed ( $SiO_2$ ; 1.5% MeOH/ $CH_2Cl_2$ ) to provide title compound (0.12 g; 65%) as a colorless oil.

15 B.



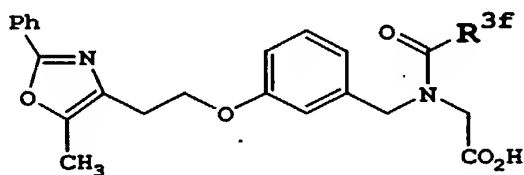
A solution of Part A compound (0.12 g, 0.22 mmol)  
 20 and LiOH (0.050 g, 2.1 mmol) in  $H_2O$ /THF (5 mL of a 40:60 solution) was stirred at RT for 12 h. The reaction mixture was concentrated in vacuo to yield an oily residue, which was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 ml/min. 30 min  
 25 continuous gradient from A:B = 50:50 to 100%B; solvent

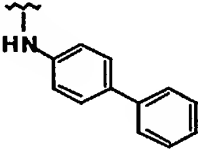
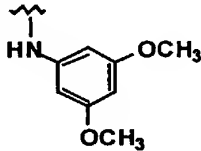
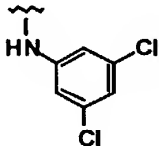
MeOH:H<sub>2</sub>O:TFA) to provide title compound (59 mg, 50%) as a colorless oil.  $[M + H]^+ = 530.3$

10

## 15

**Table 8: (Urea-Acids)**



Example No.	R <sup>3f</sup>	[M+H] <sup>+</sup>
395		562.3
396		546.3
397		554.2

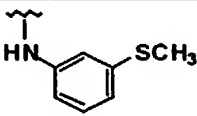
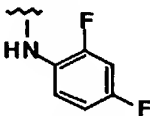
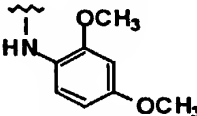
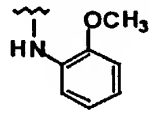
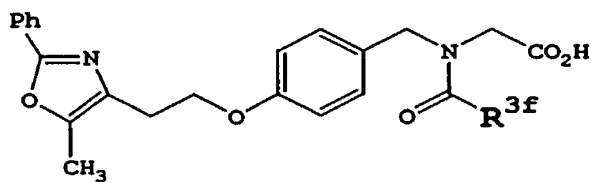
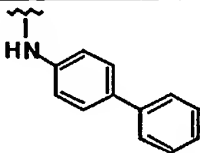
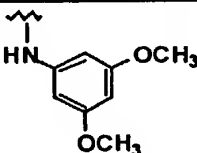
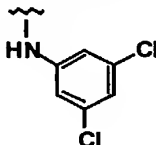
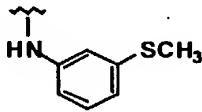
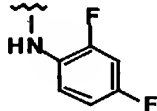
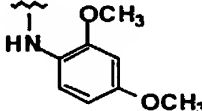
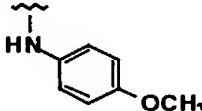
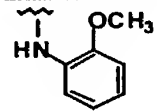
Example No.	$R^{3f}$	$[M+H]^+$
398		532.3
399		522.3
400		546.3
401		516.3

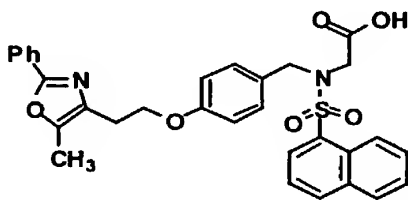
Table 9: (Urea-Acids)



5

Example No.	$R^{3f}$	$[M+H]^+$
402		562.3
403		546.3
404		554.2

Example No.	R <sup>3f</sup>	[M+H] <sup>+</sup>
405		532.3
406		522.3
407		546.3
408		516.3
409		516.3

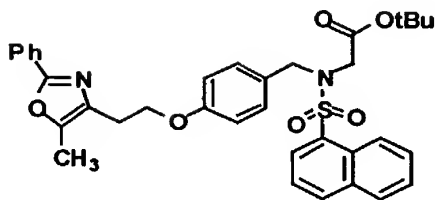
Example 410

5

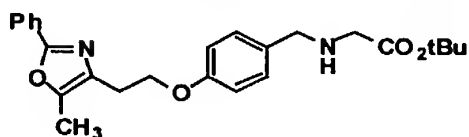
The title compound was prepared as part of a solution phase library run using the following procedure:

10

A.



5 To a mixture of 1-naphthylsulfonyl chloride (26.8 mg, 0.12 mmol) and DMAP (2 mg, 0.016 mmol) in pyridine (2 mL) was added a solution of the amino-t-butyl ester



(prepared as described in Example 8)

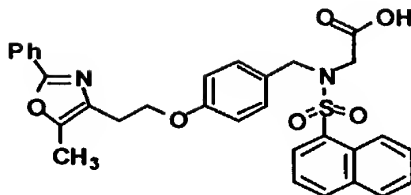
10 (20 mg, 0.05 mmol) in pyridine (0.6 mL). The reaction was stirred at RT for 20 h. Resin-bound amine (WA21J, Supelco; 5.8 mmol/g loading; 150 mg) was added to the mixture. The reaction was stirred for a further 4 h. The resin was filtered off and the filtrate was  
15 concentrated *in vacuo* to give the crude product, which was chromatographed (CUSIL12M6 column; United technology; 2 g of sorbent in a 6 mL column) by the procedure outlined below.

20 1) The column was conditioned with hexane (20 mL).

2) The residue was dissolved in a minimal volume of EtOAc and loaded onto the silica gel column.

25 3) The cartridge was eluted with Hex/EtOAc(3:1),  
Hex/EtOAc (1:1). The desired fraction (identified by  
TLC) was collected and concentrated to give title  
compound as a viscous oil which was used in the next step  
without any further purification.

B.

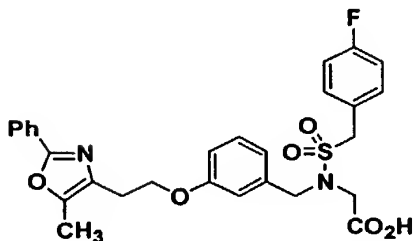


5 Et<sub>3</sub>N ((0.3 ml of a 1M solution in CH<sub>2</sub>Cl<sub>2</sub>) and TMSI  
(0.3 ml of a 1M solution in CH<sub>2</sub>Cl<sub>2</sub>) were successively  
added to a solution of Part A compound in CH<sub>2</sub>Cl<sub>2</sub>. The  
reaction mixture was stirred at RT for 12h and then was  
concentrated *in vacuo* to give the crude product. The  
10 product was purified by solid-phase extraction using a  
CHQAX12M6 column (United technology; 2 g of sorbent in a  
6 mL column) by the procedure outlined below.

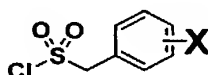
- 15 1) The column was conditioned with CH<sub>2</sub>Cl<sub>2</sub> (25 mL).
- 2) The residue was dissolved in a minimal volume of CH<sub>2</sub>Cl<sub>2</sub>  
and loaded onto the SAX column.
- 3) The cartridge was washed successively with CH<sub>2</sub>Cl<sub>2</sub> (25  
20 mL), CH<sub>2</sub>Cl<sub>2</sub>/MeOH (5% MeOH, 15 mL), CH<sub>2</sub>Cl<sub>2</sub>/MeOH (50% MeOH,  
15 mL), MeOH (20 mL).
- 4) The product was eluted with a solution of 1% TFA in  
MeOH (20 mL).

25 The final product-containing fraction was collected  
and concentrated *in vacuo* using a Speed Vac to afford  
BMS-329075 (16 mg; 62%). Reverse-phase analytical HPLC  
indicated that the product purity was 90%. In addition,  
30 LC/MS (electrospray) gave the correct molecular ion  
[(M+H)<sup>+</sup> = 557.1] for the desired compound.

### Example 411



A.

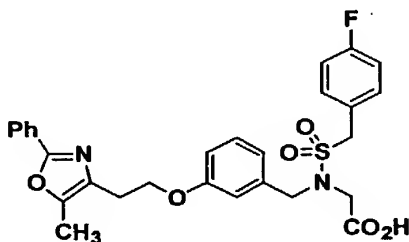


(X = halogen, alkyl, CF<sub>3</sub>, CF<sub>3</sub>O, etc.)

10           The following general procedure was utilized for the  
preparation of the requisite substituted benzyl sulfonyl  
chlorides:

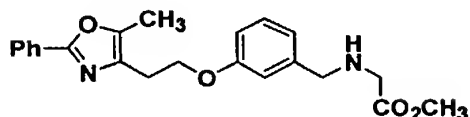
Cl<sub>2</sub> gas was bubbled into a 0°C solution of 4-  
15 fluorobenzyl mercaptan (1.0 g, Lancaster) in glacial  
acetic acid (100 mL) and H<sub>2</sub>O (5.0 mL) for 1h. The  
reaction mixture was then poured into ice-H<sub>2</sub>O and  
immediately extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL); the organic  
phase was cautiously washed successively with H<sub>2</sub>O (200  
20 mL), aqueous saturated NaHCO<sub>3</sub> (2 x 100 mL), and finally  
brine (200 mL). The organic phase was dried (MgSO<sub>4</sub>) and  
concentrated in vacuo to furnish 4-fluorobenzyl sulfonyl  
chloride as a colorless solid (1.3 g; 89%).

25 B.





To a solution of the secondary amine methyl ester  
(25 mg; 0.066 mmol)

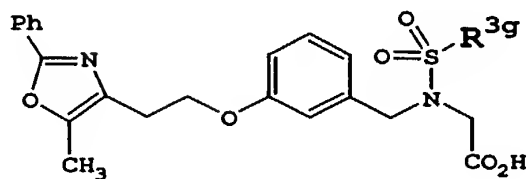


- 5 (prepared as described in Example 6),  
in pyridine (0.8 mL) was added 4-fluorobenzyl sulfonyl  
chloride (68 mg; 0.33 mmol; 5 equiv). The mixture was  
heated to 75°C, stirred overnight at 75°C, and then  
concentrated in vacuo. The black residue was treated  
10 with aqueous LiOH (1.0 mL of a 0.3 M solution) in  
H<sub>2</sub>O/MeOH/THF for 18 h, then concentrated in vacuo. The  
residue was acidified with 1.0 M aqueous HCl to pH = 1-2  
and extracted with EtOAc (2x), dried (Na<sub>2</sub>SO<sub>4</sub>) and  
concentrated in vacuo to give the crude product.  
15 Purification by preparative HPLC (YMC S5 ODS 20mm x 250  
mm reverse-phase column; 15 min continuous gradient from  
60:40 A:B to 100% B with 10 min hold time, where A =  
90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA;  
flow rate = 25 mL/min) gave the title compound (12 mg;  
20 34%) as a white solid. [M + H]<sup>+</sup> (LC/MS) = 539.1

#### Examples 412 to 456

Utilizing one of the above procedures, the analogs  
in Tables 10 and 11 were synthesized.

**Table 10: (Sulfonamide-Acids)**



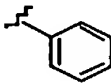
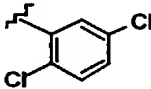
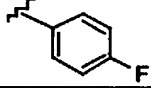
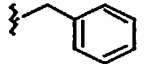
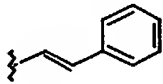
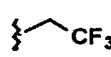
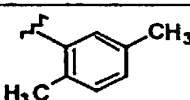
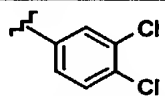
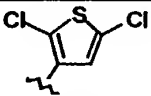
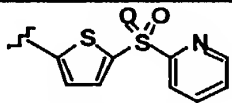
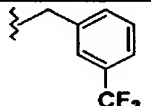
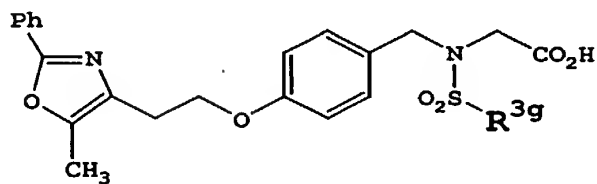
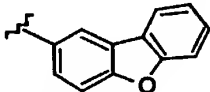
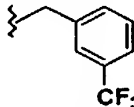
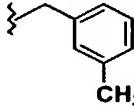
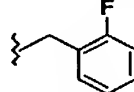
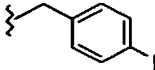
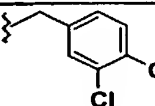
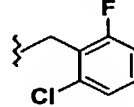
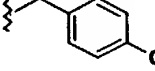
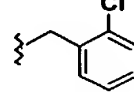
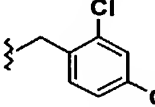
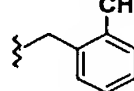
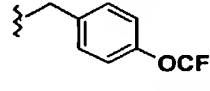
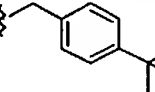
Example No.	R <sup>3g</sup>	[M+H] <sup>+</sup>
412		507.3
413		575.2
414		525.2
415		521.2
416		533.2
417		513.2
418		535.3
419		575.2
420		581.1
421		590.3
422		589.2

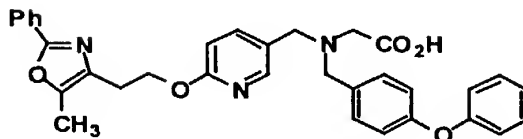


Table 11: (Sulfonamide-Acids)

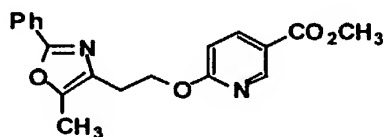


Example No.	R <sup>3g</sup>	[M+H] <sup>+</sup>
434		549.4
435		557.3
436		506.3
437		549.3
438		541.2
439		521.3
440		533.3
441		535.4
442		575.3
443		678.3

Example No.	R <sup>3g</sup>	[M+H] <sup>+</sup>
444		597.4
445		589.2
446		535.3
447		539.1
448		539.1
449		589.0
450		573.2
451		555.2
452		555.3
453		589.2
454		535.3
455		605.3
456		577.4

Example 457

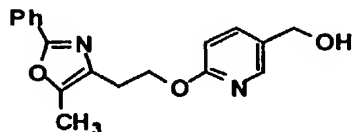
A.



5

To a 0°C solution of methyl 2-hydroxypyridine-5-carboxylate (0.2 g, 1.3 mmol), 2-(5-methyl-2-phenyl  
10 oxazol-4-yl)ethanol (0.32 g, 1.56 mmol) and Ph<sub>3</sub>P (0.38 g, 1.56 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added DEAD (0.2 mL, 1.95 mmol) dropwise and the reaction was stirred at 25°C for 12 h. The solution was concentrated *in vacuo*, and chromatographed on SiO<sub>2</sub> (4:1 hex:EtOAc) to provide title  
15 compound (0.28 g, 63%) as an oil.

B.

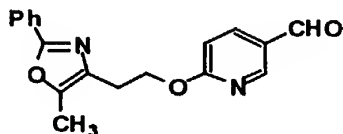


20

To a -78°C solution of Part A compound (0.28g., 0.82 mmol) in THF (10 mL) was added DIBALH (2.0 mL of a 1 M solution in CH<sub>2</sub>Cl<sub>2</sub>; 1.95 mmol) and the reaction was stirred at -78°C for 4 h. TLC of an aliquot of the  
25 reaction showed the presence of both the corresponding aldehyde and alcohol. The reaction was warmed to 25°C and stirred at RT for 1 h, after which only the alcohol was observed by TLC. The reaction was quenched with water and diluted with EtOAc. The organic layer was  
30 washed with brine, dried (MgSO<sub>4</sub>), and concentrated in

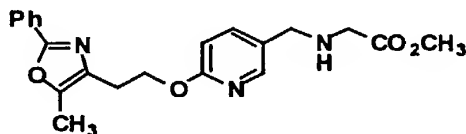
vacuo to furnish title compound as an oil. This crude material was used in the next reaction without further purification.

5 C.



To a  $-78^{\circ}\text{C}$  solution of oxalyl chloride (0.22 mL, 2.6 mmol) and DMSO (0.37 mL, 5.2 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL) was added dropwise a solution of Part B compound (0.42 g of crude material in 5 mL  $\text{CH}_2\text{Cl}_2$ ). The reaction mixture was stirred for 2 h at  $-78^{\circ}\text{C}$  and then  $\text{Et}_3\text{N}$  (1 mL) was added dropwise. The reaction mixture was stirred for an additional 0.5 h at  $-78^{\circ}\text{C}$  and then was slowly warmed to  $25^{\circ}\text{C}$ . The reaction mixture was diluted with EtOAc (200 mL) and washed successively with aqueous  $\text{NaHCO}_3$  and brine. The organic layer was dried ( $\text{MgSO}_4$ ), then concentrated in vacuo to provide title compound (0.40 g; 95%) as an oil, which was used in the next step without further purification.

D.



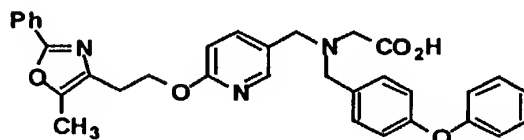
25

A mixture of Part C compound (<0.82 mmol), glycine methyl ester hydrochloride (0.5g., 4.0 mmol),  $\text{NaBH}(\text{OAc})_3$  (0.85g., 4.0 mmol) and DCE (10 mL) was stirred at  $25^{\circ}\text{C}$  for 12 h. The reaction mixture was then diluted with EtOAc (50 mL) and washed successively with aqueous  $\text{NaHCO}_3$  and brine. The organic layer was dried ( $\text{MgSO}_4$ ), then concentrated in vacuo to give title compound (0.31 g;

82%) as an oil (>95% pure by analytical reverse-phase HPLC) which was used in the next step without further purification.

5

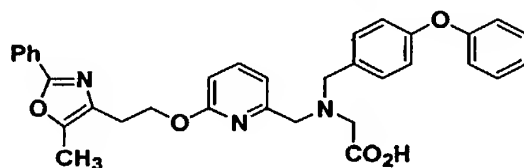
E.



A mixture of Part D compound (0.050 g; 0.13 mmol),  
10 4-phenoxybenzaldehyde (0.048 g; 0.26 mmol), NaBH(OAc)<sub>3</sub>  
(0.082 g; 0.39 mmol) in DCE (10 mL) was stirred at 25°C  
for 12 h. The reaction mixture was diluted with EtOAc  
(50 mL) and washed successively with aqueous NaHCO<sub>3</sub> and  
brine. The organic layer was dried (MgSO<sub>4</sub>), then  
15 concentrated in vacuo to give the tertiary amino methyl  
ester as an oily residue. To this residue, LiOH (0.050  
g) and H<sub>2</sub>O/THF (2 mL of a 60/40 solution) were added and  
the reaction was stirred at RT for 12 h. Preparative  
HPLC (YMC S5 ODS 30 x 250mm column - continuous gradient  
20 over 30 min; flow rate = 25 mL/min from 30:70 A:B to  
100% B; A = 90:10:0.1 H<sub>2</sub>O:MeOH:CF<sub>3</sub>CO<sub>2</sub>H; B = 90:10:0.1  
MeOH:H<sub>2</sub>O:CF<sub>3</sub>CO<sub>2</sub>H) provided title compound (0.021 g; 30%)  
as a TFA salt.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 8.18 (s, 1H), 7.94 (d, 6.6 Hz, 2H),  
7.86 (d, 8.8 Hz, 1H), 7.45 (m, 3H), 7.34 (m, 3H), 7.14  
(t, 7.4 Hz, 1H), 7.02-6.92 (m, 5H), 6.81 (t, 8.8 Hz, 1H),  
4.51 (m, 6H), 3.59 (s, 2H), 3.06 (t, 6.2 Hz, 2H)

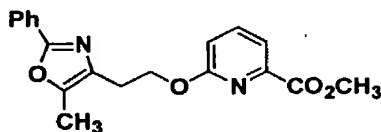
30

Example 458

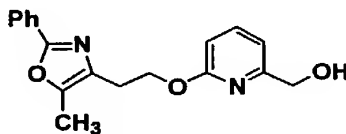


COC(=O)c1cc(O)ccn1

15 B.

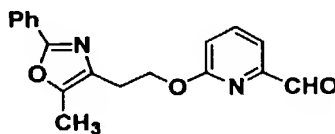


C.



To a solution of Part B compound (0.92 g, 2.7 mmol) in THF (50 mL) was added  $\text{LiAlH}_4$  (5 mL of a 1.0 M solution in THF, 5 mmol) dropwise at  $-78^\circ\text{C}$  and the resulting reaction was allowed to warm to  $0^\circ\text{C}$  over 2 h. The  
5 reaction was then quenched by adding a few pieces of ice into the mixture. The reaction mixture was partitioned between EtOAc (200 mL) and brine (50 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give an oil (0.92 g; 95%) which was used in the next reaction  
10 without further purification.

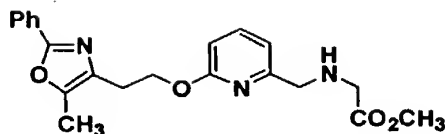
D.



15

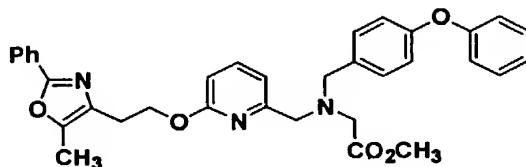
To a solution of oxalyl chloride (0.47 mL, 5.4 mmol) and DMSO (0.36 mL, 10.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL) was added dropwise a solution of Part C compound (0.92 g; >2.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $-78^\circ\text{C}$ . The reaction mixture  
20 was stirred for 2 h and then  $\text{Et}_3\text{N}$  (1 mL) was added dropwise. The reaction mixture was allowed to stir for an additional 0.5 h at  $-78^\circ\text{C}$  and then slowly warmed to  $25^\circ\text{C}$ . The reaction mixture was then diluted with EtOAc (200 mL) and washed successively with aqueous  $\text{NaHCO}_3$  and  
25 brine. The organic layer was dried ( $\text{MgSO}_4$ ) and then concentrated in vacuo to yield title compound (0.90 g; >90% pure by  $^1\text{H}$  NMR analysis) as an oil. This material was used in the next step without further purification.

E.



5 To a solution of Part D compound (0.90g; 2.7 mmol),  
glycine methyl ester hydrochloride (1.7 g, 13.5 mmol) in  
1,2 dichloroethane (10 mL) was added NaBH(OAc)<sub>3</sub> (1.7 g,  
8.1 mmol) in one portion. The resulting solution was  
10 stirred at 25°C for 12 h. The reaction mixture was  
concentrated in vacuo to give an oil, which was  
chromatographed (SiO<sub>2</sub>; 30% acetone in hexane) to provide  
title compound (0.86 g; 83%) as a colorless oil.

F.

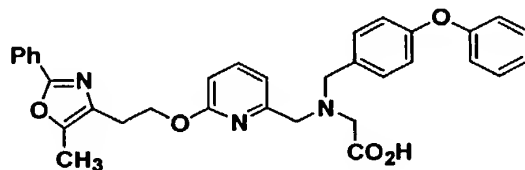


15

A solution of Part E compound (0.040 g, 0.1 mmol),  
4-phenoxybenzaldehyde (0.030 g, 0.15 mmol) and NaBH(OAc)<sub>3</sub>  
20 (0.060 g, 0.3 mmol) in DCE (10 mL) was stirred at RT for  
12 h. The reaction mixture was concentrated in vacuo and  
the oily residue was chromatographed (SiO<sub>2</sub>; 30% acetone  
in hexane) to provide the amino-ester title compound (56  
mg; >95%) as a colorless oil.

25

G.



10

15

## 20

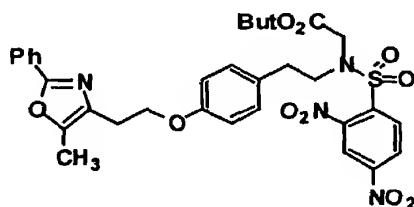


30

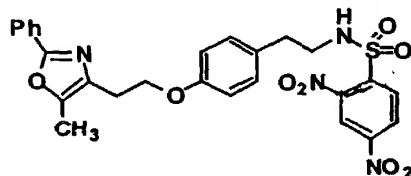
The reaction mixture was concentrated *in vacuo*, and the residue was chromatographed ( $\text{SiO}_2$ ; stepwise gradient from 95:5 to 4:1 hex:EtOAc) to obtain title compound (1.43 g, 65%).

5

B.

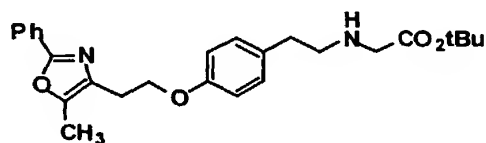


- 10 A solution of Part A compound (1.01 g, 2.37 mmol) and TFA (8 mL) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was stirred at RT for 4.5 h. The solution was concentrated *in vacuo*, and the residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and filtered through a pad of solid  $\text{K}_2\text{CO}_3$ . The filtrate was concentrated *in vacuo* to give the corresponding crude amine. To a solution of the
- 15 crude amine in THF (11.9 mL) were added pyridine (0.383 mL, 4.74 mmol) and 2,4-dinitrobenzenesulfonyl chloride (0.85 g, 3.19 mmol) and the solution was stirred at RT for 15h. Since some starting material still remained at
- 20 this point, more sulfonyl chloride (0.32 g, 1.2 mmol) was then added. After a further 4 h, HPLC analysis indicated that all starting material had been consumed. The reaction mixture was diluted with  $\text{Et}_2\text{O}$ , washed with 1N aq HCl, saturated aq  $\text{NaHCO}_3$  and brine, dried ( $\text{MgSO}_4$ ),
- 25 filtered and concentrated *in vacuo* to provide the crude 2,4-dinitrobenzenesulfonamide



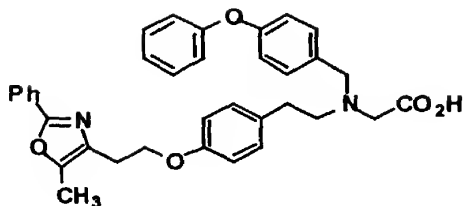
To a solution of the crude 2,4-dinitrobenzene-sulfonamide in CH<sub>3</sub>CN (3 mL) were added K<sub>2</sub>CO<sub>3</sub> (excess) and tert-butyl bromoacetate (7.11 mmol). The reaction was stirred at RT overnight. HPLC analysis indicated the ratio of product to starting material was 2/1. More DMF (3 mL), K<sub>2</sub>CO<sub>3</sub> and tert-butyl bromoacetate were added to the reaction mixture. The reaction was complete in 2 h. The reaction mixture was diluted with Et<sub>2</sub>O, washed with 1N aq HCl, saturated NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to provide the crude tert-butyl ester. This crude material was chromatographed (SiO<sub>2</sub>; hexanes/EtOAc; stepwise gradient from 9:1 to 2:1) to give title compound (0.663 g, 42% overall).

C.



To a solution of Part B compound (0.663 g, 0.995 mmol) in THF (2.5 mL) were added Et<sub>3</sub>N (0.208 mL, 1.49 mmol) and mercaptoacetic acid (0.090 mL, 1.29 mmol). The reaction was stirred at RT overnight. The reaction mixture was then diluted with Et<sub>2</sub>O, washed with 1N aq HCl, saturated NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>), and concentrated *in vacuo*. The residue was chromatographed (SiO<sub>2</sub>; hexanes/EtOAc; stepwise gradient from 9:1 to 2:1) to give title compound (0.265 g, 61%).

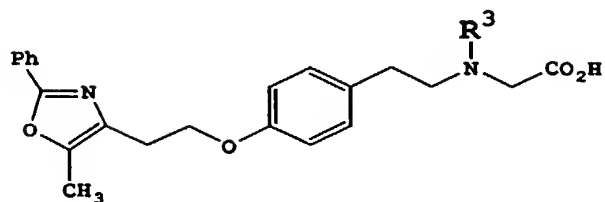
D.


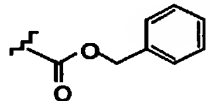
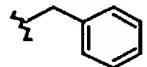


5 To a solution of Part C compound (0.015 g, 0.0344 mmol) in DCE (1 mL) were added 4-phenoxybenzaldehyde (0.103 mmol) and NaBH(OAc)<sub>3</sub> (0.0365 g, 0.172 mmol). The reaction was stirred at RT for 15 h. The reaction mixture was filtered through a cotton plug to provide a clear solution, which was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated aq NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>), and concentrated *in vacuo*. The crude product was purified by preparative HPLC (YMC S5 ODS 30x250 mm column: flow rate 25 mL/min, gradient 20%B to 100%B over 25 min, 100%B hold for 15 min, Retention time = 29.1 min) to furnish the tert-butyl ester. A solution of this material was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.3 mL) and TFA (0.5 mL) was added slowly. The reaction was stirred at RT overnight and was then concentrated *in vacuo*. The residue was then dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with H<sub>2</sub>O, saturated aq NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give title compound (0.012 g, 61%). LC/MS gave the correct [M + H]<sup>+</sup> = 563.3

Further analogs (as shown in the table below) were synthesized by the same reductive amination procedure as described in Example 459 Part D using Example 459 Part C compound and different aromatic aldehydes. In addition carbamate-acids such as Example 461 compound were also synthesized using the general method described previously for the synthesis of the Example 136 compound.

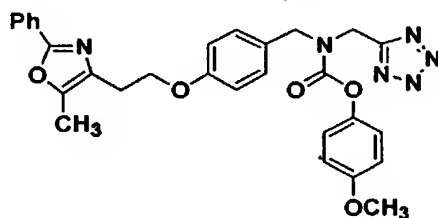
Table 12



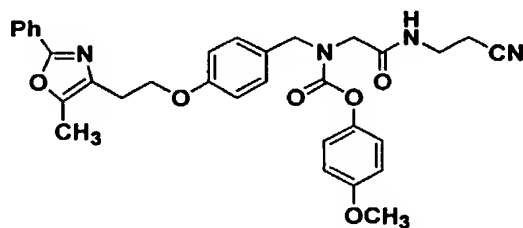
Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
460		571.3
461		515.3
462		471.3

5

### Example 463



A.



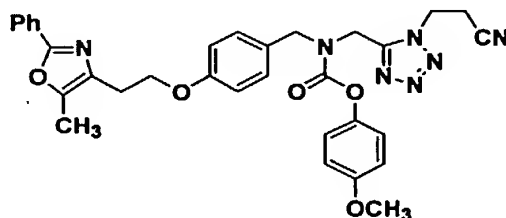
10

To a solution of the Example 230 acid (240 mg, 0.47 mmol) in DMF (2.0 mL) were added HOAT (68 mg, 0.49 mmol),  
15 EDAC (94 mg, 0.49 mmol) and 2-cyanoethylamine (34 mg, 0.49 mmol). The solution was stirred at RT for 18 h;



analysis of the reaction by LC-MS showed that starting material was still present. Additional 2-cyanoethylamine (34 mg, 0.49 mmol) was added and the reaction mixture was stirred at RT for 48 h. Volatiles were removed in vacuo and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and washed successively with water (2 x 30 mL) and brine (30 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. The resulting white residue was dissolved in a minimum amount of CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and precipitation by the cautious addition of EtOAc furnished the amide product title compound (184 mg; 70%) as a white solid.

B.



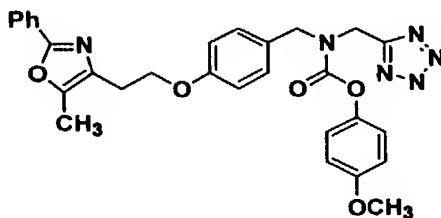
15

To a 0°C solution of Part A compound (180 mg; 0.32 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) were successively added Ph<sub>3</sub>P (83 mg; 0.32 mmol), DEAD (100 µL, 0.64 mmol) and TMSN<sub>3</sub> (85 µL, 0.64 mmol). The reaction mixture was stirred at RT for 24 h. LC-MS analysis showed that a significant amount of starting material still remained. The reaction mixture was then concentrated in vacuo to 2/3 of the original volume and additional Ph<sub>3</sub>P, DEAD and TMSN<sub>3</sub> (1 equivalent of each reagent) were added. The reaction mixture was stirred at RT for another 24h and then diluted with EtOAc (40 mL). The solution was treated with 5% aqueous CAN solution (10 mL) and stirred for 15 min. The reaction solution was washed with water (30 mL) and brine (30 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was

30

chromatographed (SiO<sub>2</sub>; ether:CH<sub>2</sub>Cl<sub>2</sub> 3:7) to furnish the title compound (100 mg; 53%) as a white solid.

C.

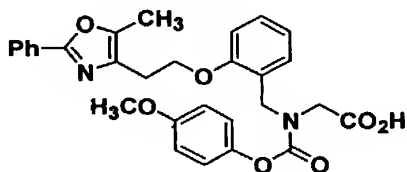


5

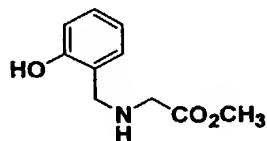
To a solution of Part B compound (100 mg, 0.17 mmol) in THF/1,4-dioxane (6:1, 1.4 mL) was added aqueous NaOH solution (0.6 mL of a 1.0 M solution, 3.5 equiv). The mixture was stirred at RT for 14 h and then acidified to ~pH 2 with 1.0 M aqueous H<sub>3</sub>PO<sub>4</sub> solution. EtOAc (30 mL) was added, and the organic phase was washed with water (15 mL) and brine (15 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the title tetrazole (35 mg; 38%) as a white foam. LC/MS (electrospray) gave the correct molecular ion: [M + H]<sup>+</sup> = 541.3

20

Example 464



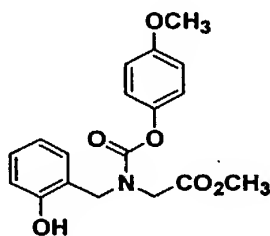
A.



25

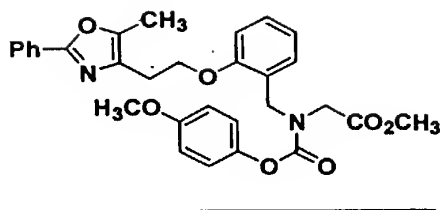
A mixture of 2-hydroxybenzaldehyde (500 mg, 4.09 mmol), glycine methyl ester hydrochloride (544 mg, 4.09 mmol) and Et<sub>3</sub>N (495 mg, 4.9 mmol) in dry MeOH (5 mL) was stirred at RT for 3 h. NaBH<sub>4</sub> (155 mg, 4.09 mmol) was then added in three portions. The reaction was stirred at RT for another 30 min. Saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (1 mL) was added to destroy the remaining NaBH<sub>4</sub> and then aqueous HCl (10 mL of a 1N solution) was added. The aqueous phase was washed with EtOAc (3 x 20 mL), then carefully basified with 1N aq NaOH to pH = 7-8. The aqueous phase was then extracted with EtOAc (3 x 20 mL). The orange-red solution was concentrated *in vacuo* to give title compound as a yellow viscous oil.

15 B.



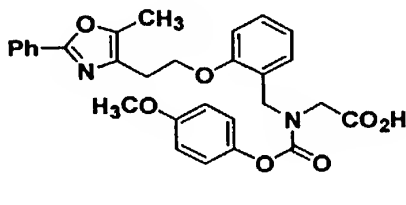
Part A compound (38 mg, 0.195 mmol), 4-methoxyphenyl chloroformate and pyridine (39 mg, 5 mmol) was dissolved in 0.1 mL CH<sub>2</sub>Cl<sub>2</sub>, for 5 min. The reaction mixture was then washed with aqueous HCl (2 x 2 mL of a 1N solution). The organic phase was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated *in vacuo* and chromatographed (SiO<sub>2</sub>; hex:EtOAc = 7 :3) to give title compound (40 mg; 59%) as a pale yellow oil.

C.



- 5 To a solution of Part B compound (40 mg, 0.116 mmol), 2-[2-phenyl-5-methyl-oxazole-4-yl]-ethanol (Maybridge; 24 mg, 0.116 mmol) and  $\text{Ph}_3\text{P}$  (40 mg, 0.151 mmol) in dry THF (3 mL) was added dropwise DEAD (26 mg, 0.151 mmol). The solution was stirred at RT overnight.
- 10 The orange-red solution was concentrated *in vacuo* and the residue was purified by Prep-HPLC (continuous gradient from 50% A:50% B to 100%B; A = 90%  $\text{H}_2\text{O}$ :10 %MeOH + 0.1% TFA); (B = 90% MeOH/10%  $\text{H}_2\text{O}$  + 0.1% TFA) for 10 min; YMC SH-343-5 ODS 20 x 100 mm (5  $\mu\text{m}$ ) column) to provide title
- 15 compound (30 mg, 47%) as a yellow viscous oil.

D.



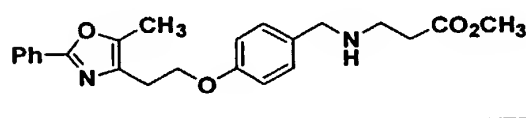
20

- Part C compound was dissolved in MeOH (3 mL) and  $\text{H}_2\text{O}$  (0.3 mL). To this solution was added LiOH (3 mg) and the reaction was stirred at RT for 3 h. Volatiles were removed *in vacuo* and the solution was acidified with 1N
- 25 aqueous HCl to pH = ~3-4. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to give title compound as a white solid (18 mg; 64%). LC/MS (electrospray) gave the
- 30 correct molecular ion  $[(\text{M}+\text{H})^+ = 516]$ .

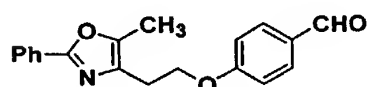
5

CC1=C(CCOc2ccc(cc2)COC(=O)NCC(=O)O)c3ccccc3O1

A.



15



20

COC(=O)CN(Cc1ccc(OCCc2c(C)c(Oc3ccccc3)n2)cc1)C(=O)Oc4ccc(Cl)cc4

- 201 -

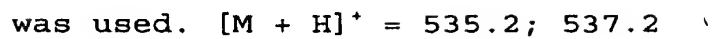
10

CC1=C(CCOc2ccc(cc2)C(=O)N(CCC(=O)O)C(=O)Oc3ccc(Cl)cc3)C(=N1)c4ccccc4

A solution of Part B compound and  $\text{LiOH} \cdot \text{H}_2\text{O}$  (5 mg) in  $\text{THF}:\text{H}_2\text{O}$  (4:1) was stirred at RT for 1 h. The reaction solution was acidified to pH 3 with aqueous  $\text{HCl}$ , then extracted with  $\text{EtOAc}$ . The combined organic extracts were concentrated in vacuo to give title compound (5 mg; 18%) as a white solid.  $[\text{M} + \text{H}]^+ = 535.2; 537.2$

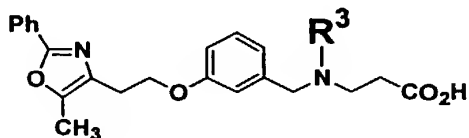
CC1=C(CCOc2ccc(cc2)CNC(=O)Oc3ccc(Cl)cc3)c2ccccc2N1

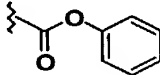
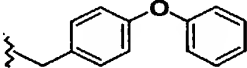
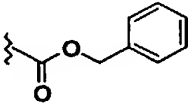
Title compound was synthesized using the same sequence as in Example 465 with the exception that the aldehyde

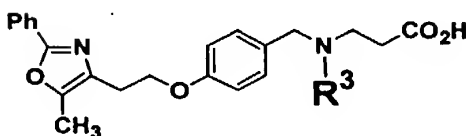


Following procedures as described above, Examples 467 to 472 compounds were prepared.

## 10



Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
467		501.3
468		563.3
469		515.3

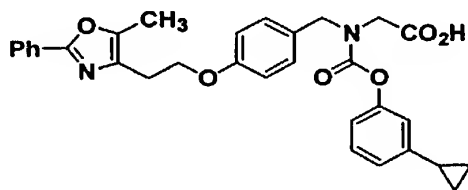
Examples 470 to 472

5

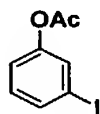
Example No.	R <sup>3</sup>	[M+H] <sup>+</sup>
470		501.3
471		563.3
472		515.3

Example 473

10



A.



15

A mixture of 3-iodophenol (2.0 g; 9.1 mmol), acetic anhydride (4.6 g; 45.5 mmol) and pyridine (3.6 g; 45.5 mmol) was stirred in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) for 3 h. The resulting mixture was washed with saturated aqueous NH<sub>4</sub>Cl

20



**B.**



C.



30

CC(=O)Oc1ccc(C#C)cc1

© 2000 Blackwell Science Ltd *Journal of Internal Medicine* 247: 399–406

CC(=O)Oc1ccc(C=C)cc1

---

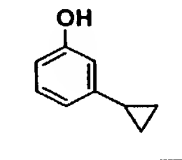
20

CC(=O)Oc1ccc(cc1)C2CC2

---

warm to RT and then stirred at RT for 3 h, after which it was partitioned between saturated aqueous  $\text{NH}_4\text{Cl}$  and EtOAc (50 mL each). The organic phase was washed with saturated aqueous  $\text{NH}_4\text{Cl}$  and  $\text{H}_2\text{O}$  (50 mL each) and concentrated in vacuo. The residue was chromatographed (5  $\text{SiO}_2$ ; hexane:EtOAc 9:1) to furnish Part F compound (230 mg; 69%) as a colorless oil.

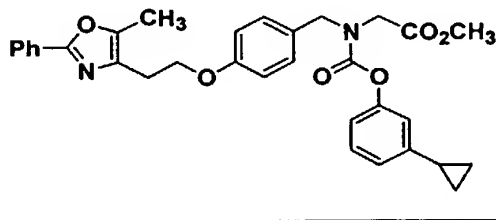
G.



10

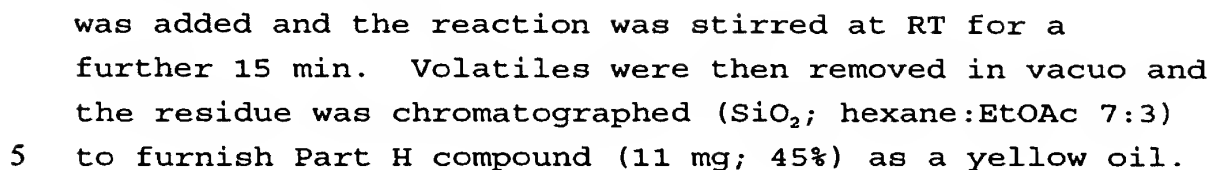
A mixture of Part F compound (100 mg; 0.57 mmol) and  $\text{K}_2\text{CO}_3$  (157 mg; 1.1 mmol) in MeOH (5 mL) was stirred at RT overnight (no reaction). Aqueous LiOH (1.1 mL of a 15 1 M solution; 1.1 mmol) was added and the solution was stirred at RT overnight. Volatiles were removed in vacuo and the residue was partitioned between aqueous 1 M HCl and EtOAc. The organic phase was concentrated in vacuo and the residue was chromatographed ( $\text{SiO}_2$ ; hexane:EtOAc 20 4:1) to furnish Part G compound (70 mg; 92%) as a yellow oil.

H.



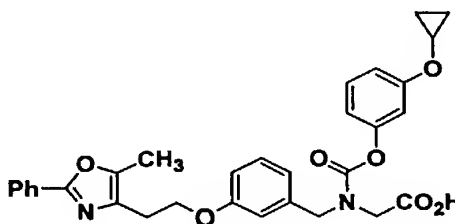
25

To a solution of Part G compound (6 mg; 0.045 mmol) in DMF (0.2 mL) was added potassium t-butoxide (5 mg; 30 0.05 mmol). The reaction was stirred for 2 min at RT, after which the carbamoyl chloride (20 mg; 0.045 mmol)

CC1=C(CCOc2ccc(cc2)COC(=O)NCC(=O)O)N=C(N1)c3ccccc3

A solution of Part H compound and  $\text{LiOH}\cdot\text{H}_2\text{O}$  in  $\text{MeOH}/\text{H}_2\text{O}$  (10 mL of a 9:1 mixture) was stirred at RT overnight. The solution was then acidified to pH ~3 with aqueous HCl and extracted with EtOAc. The combined organic extracts were concentrated in vacuo and purified by preparative HPLC to give title compound (10.1 mg; 95%) as an off-white lyophilate.  $[\text{M} + \text{H}]^+ = 527.3$

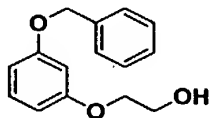
## 20

CCOC(=O)COc1ccccc1Oc2ccccc2

- 208 -

A mixture of 3-benzyloxybenzaldehyde (2.00 g; 1.0 mmol), ethyl bromoacetate (1.67 g; 1.0 mmol) and  $\text{Cs}_2\text{CO}_3$  (3.25 g; 1.0 mmol) in DMF (20 mL) was stirred at RT for 8 h. The reaction mixture was partitioned between  $\text{H}_2\text{O}$  (300 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; 85:15 hex:EtOAc) to obtain Part A compound (3.48 g; >100%) as a colorless oil.

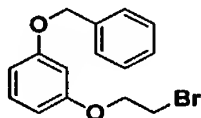
B.



15

To a solution of Part A compound (3.4 g; 11.9 mmol) in dry THF (50 mL) under Ar was added  $\text{LiAlH}_4$  (36 mL of a 0.5 M solution in THF; 17.8 mmol) dropwise. The reaction was stirred at RT for 1 h. The reaction was quenched by slow addition of saturated aqueous  $\text{NH}_4\text{Cl}$  (1 mL). Volatiles were removed in vacuo and the residue was partitioned between EtOAc (100 mL) and 1 M aqueous HCl. The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give Part B compound (2.4 g; 98%) as a white solid.

C.

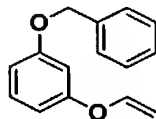


30

To a solution of Part B compound (2.4 g; 9.8 mmol) and  $\text{Ph}_3\text{P}$  (3.1 g; 14.7 mmol) in  $\text{CH}_2\text{Cl}_2$  was added  $\text{CBr}_4$  (4.80 g; 14.7 mmol). The reaction was stirred at RT overnight, then concentrated in vacuo. The residue was

chromatographed ( $\text{SiO}_2$ ; 95:5 hex:EtOAc) to give Part C compound (2.8 g; 93%) as a white solid.

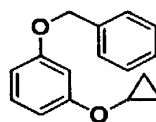
D.



5  
10 A mixture of Part C compound (310 mg; 1.0 mmol) and potassium tert-butoxide (113 mg; 2.0 mmol) in toluene (20 mL) was heated at 105°C for 20 min. Additional K<sub>2</sub>OtBu (56 mg; 1.0 mmol) was added and the reaction heated at 105°C for another 10 min. The mixture was cooled to RT and partitioned between H<sub>2</sub>O (100 mL) and EtOAc (100 mL). The organic phase was washed with H<sub>2</sub>O (2 x 100 mL), dried  
15 ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The reaction was repeated with additional Part C compound (500 mg; 1.63 mmol) and K<sub>2</sub>OtBu (182 mg; 16 mmol). The combined crude reaction products were chromatographed ( $\text{SiO}_2$ ; hexane) to give Part D compound (590 mg; 89%) as a colorless oil.

20

E.

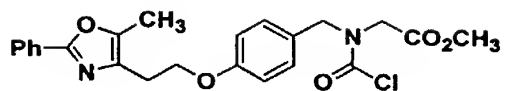


25 To a 0°C solution of Part D compound (1.4 g; 62 mmol) in DCE (100 mL) was added neat diethylzinc (1.6 mL; 16 mmol) dropwise, followed by  $\text{ICH}_2\text{Cl}$  (5.46 g; 31 mmol). The reaction mixture was allowed to warm to RT and stirred at RT overnight, then washed with 1M aqueous HCl.  
30 The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The crude residue was chromatographed twice ( $\text{SiO}_2$ ; hexane) to give Part E compound (510 mg; 30%) in addition to recovered starting material Part D compound (250 mg; 18%).









(prepared as described in Examples 6 and 139) followed by LiOH/H<sub>2</sub>O hydrolysis in the same manner as in Example 474.

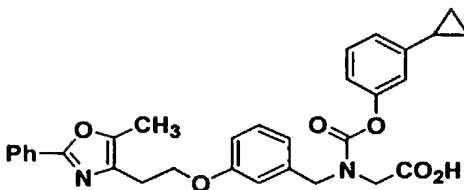
- 5 The title compound was isolated and purified as a colorless oil (340 mg; 92% over 2 steps). [M + H]<sup>+</sup> = 543.3



- 214 -



### Example 492



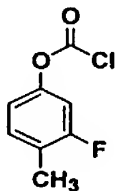
5

Example 492 was synthesized according to the procedures described hereinbefore.

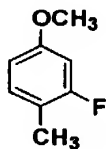
<sup>1</sup>H NMR (CDCl<sub>3</sub>; 400 MHz): δ 0.68 (t, J = 4.4 Hz; 2H), 0.94 (t, J = 4.4 Hz; 2H), 1.87 (m, 1H), 2.42 (s, 3H), 3.06 (s, 2H), 4.02 (t, J = 5.2 Hz, 2H), 4.22 (t, J = 5.2 Hz, 2H), 4.60 (2 peaks, 2H), 6.84-6.89 (m, 4H), 7.15-7.26 (m, 4H), 7.40-7.47 (m, 3H), 7.98-8.00 (m, 2H).

15           The required (commercially unavailable) phenols and chloroformates for the synthesis of the above carbamate-acid analogs were prepared as follows:

3-Fluoro-4-methyl-phenyl chloroformate



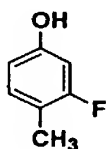
A.



25 A mixture of 5-methoxy-2-methyl aniline (5.0 g; 36 mmol), HCl (7.6 mL of a 12 M solution; 91 mmol) and H<sub>2</sub>O (11 mL) was heated at 60°C for 15 min until complete dissolution had occurred. The reaction was cooled to 0°C

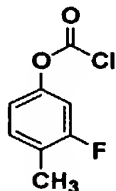
and an aqueous solution of  $\text{NaNO}_2$  (2.5 g; 36 mmol) was added dropwise (internal temperature  $\leq 7^\circ\text{C}$ ). The reaction was stirred at  $0^\circ\text{C}$  for 30 min and a  $0^\circ\text{C}$  solution of  $\text{HBF}_4$  (5.3 mL of a 48% solution; 40 mmol) was added cautiously. The reaction was stirred at  $0^\circ\text{C}$  for 20 min, and the resultant brown solid was filtered, washed with ice water (3 x 10 mL) and  $\text{H}_2\text{O}$  (2 x 10 mL). The solid was dried under high vacuum for 20 h, then heated (heat gun) until evolution of  $\text{BF}_3$  (white fumes) had ceased. The resulting brown oil was partitioned between  $\text{EtOAc}$  and  $\text{H}_2\text{O}$ . The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo and distilled by Kugelrohr to give 3-fluoro-4-methyl anisole (1.6 g; 31%) as a colorless oil.

15 B.



To a -70°C solution of 3-fluoro-4-methyl anisole (1.62 g; 11.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise BBr<sub>3</sub> (10 mL; 12 mmol). The reaction mixture was stirred at -70°C for 10 min, then allowed to warm to 0°C and stirred at 0°C for 2 h. The reaction was allowed to warm to RT and concentrated in vacuo and the residue was partitioned between H<sub>2</sub>O and EtOAc. The organic phase was washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give 3-fluoro-4-methyl phenol (1.1 g; 75%) as an oil.

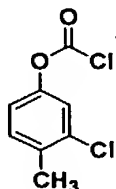
C.



30 A solution of 3-fluoro-4-methyl phenol (1.1 g; 8.7 mmol), phosgene (5.9 mL of a 1.93 M solution in toluene;

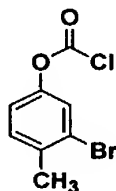
5

## 10



15

## 20

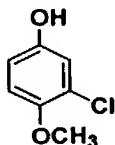


25

5

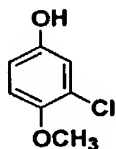
10

## 15



20

## 30

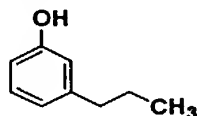


g; 59 mmol) and m-chloroperbenzoic acid (50% purity; 30

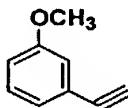
g; 89 mmol) in  $\text{CH}_2\text{Cl}_2$  (300 mL) was stirred at RT overnight. The solution was washed with saturated aqueous  $\text{Na}_2\text{CO}_3$ , then filtered through a pad of  $\text{SiO}_2$  ( $\text{CH}_2\text{Cl}_2$  as eluent) and finally chromatographed ( $\text{SiO}_2$ ; hex:EtOAc 4:1) to give the crude product (3'-fluoro-4'-methoxy phenyl acetate; 63 g). A solution of this crude material and  $\text{LiOH}\cdot\text{H}_2\text{O}$  (5 g; 120 mmol) in  $\text{MeOH}:\text{H}_2\text{O}$  (100 mL of a 9:1 mixture) was stirred at RT overnight. Volatiles were removed in vacuo, and the residue was partitioned between excess aqueous 1 M  $\text{HCl}$  and EtOAc (aqueous layer pH~3). The aqueous phase was extracted with EtOAc (2x). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give 3-fluoro-4-methoxy phenol (6.1 g; 72%) as an oil.

3-bromo-4-methoxy phenol (4.39 g; 47% for 2 steps) was synthesized using the exact analogous sequence starting from 3-bromo-4-methoxy benzaldehyde.

3-propyl phenol



A.



A mixture of 3-iodoanisole (2 g; 8.5 mmol), trimethylsilylacetylene (1.67 g; 17 mmol),  $\text{CuI}$  (32 mg; 0.17 mmol) and  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  (59 mg; 0.085 mmol) in diethylamine (10 mL) was stirred at RT for 1 h. Volatiles were removed in vacuo, and the residue was partitioned between EtOAc and brine. The organic phase was washed with brine (2 x 10 mL) and then filtered through a pad of  $\text{SiO}_2$ . Volatiles were removed in vacuo to give the crude product (3-trimethylsilylethynyl anisole)



5

COc1ccccc1C#CC

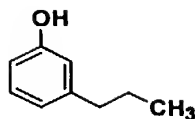
15

20

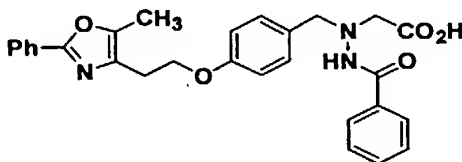
COc1ccc(CCC)cc1

30

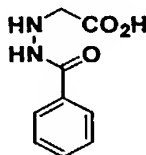
D.



To a  $-78^{\circ}\text{C}$  solution of Part C compound (1.0 g; 6.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added  $\text{BBr}_3$  (4.8 mL of a 1 M solution in  $\text{CH}_2\text{Cl}_2$ ). The reaction was allowed to warm to RT and was stirred at RT for 3 h, after which it was cautiously partitioned between aqueous 1 M  $\text{HCl}$  and  $\text{CH}_2\text{Cl}_2$ . The organic phase was washed with aqueous  $\text{NH}_4\text{Cl}$ , dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give 3-propyl phenol (900 mg; 100%) as a yellow oil.

Example 495

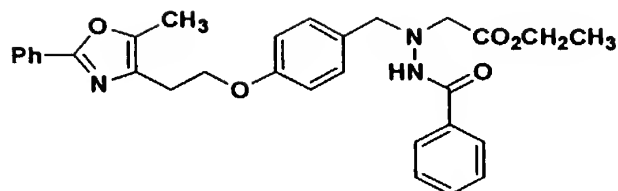
A.



20

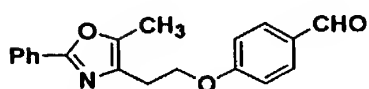
A mixture of benzoic acid (1.22 g; 10 mmol), methanesulfonyl chloride (1.15 g; 10 mmol),  $\text{K}_2\text{CO}_3$  (5.52 g; 40 mmol) and benzyltriethylammonium chloride (0.23 g; 1 mmol) in toluene was stirred at  $80^{\circ}\text{C}$  for 2 h. Ethyl hydrazine acetate hydrochloride (1.55 g; 10 mmol) was then added and the reaction was stirred for a further 30 min, then cooled to RT. Solids were filtered off and the filtrate was concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; stepwise gradient from 3:1 to 1:1 hexane:EtOAc) to give Part A compound (350 mg; 16%) as a white solid.

B.



5

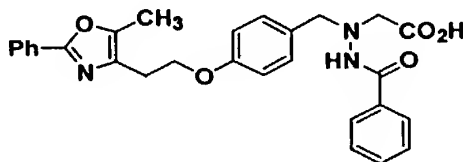
To a 0°C solution of Part A compound (49 mg; 0.22 mmol) and the aldehyde (50 mg; 0.10 mmol)



- 10 in DCE (3 mL) was added NaBH(OAc)<sub>3</sub> (30 mg; 0.42 mmol). The reaction was allowed to warm to RT and stirred at RT for 2 h, then at 60°C for 18 h. The mixture was cooled to RT and concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm
- 15 column; flow rate = 25 mL/min; 20 min continuous gradient from 70:30 B:A to 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Part B compound.

20

C.



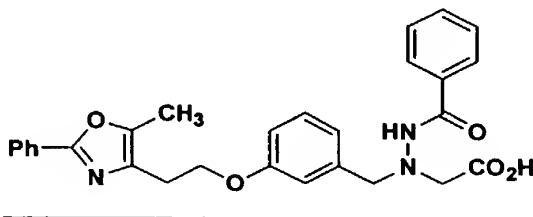
- A solution of crude Part B compound in THF (1 mL) and aqueous LiOH (0.3 mL of a 1 M solution; 0.3 mmol) was stirred at RT for 3 h, then acidified to pH ~3 with aqueous 1 M HCl. The aqueous phase was extracted with EtOAc (2x); the combined organic extracts were concentrated in vacuo. The residue was purified by
- 30 preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 mL/min; 22 min continuous gradient from 70:30 B:A to

100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give title compound (26 mg; 33% yield over 2 steps) as a white solid.

[M + H]<sup>+</sup> = 486.3

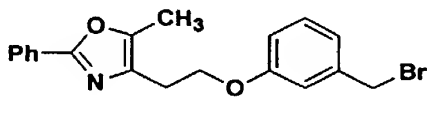
5

Example 496



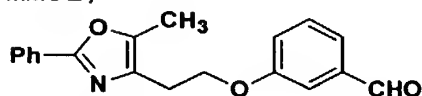
10

A.



15

To a 0°C solution of the aldehyde (200 mg; 0.65 mmol)



20

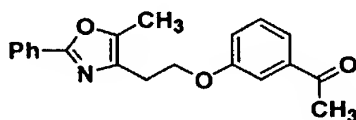
in MeOH (2 mL) was added portionwise NaBH<sub>4</sub> (24 mg; 0.65 mmol), after which the reaction was allowed warm to RT and stirred at RT for 1 h. Volatiles were removed in vacuo and the residue was partitioned between H<sub>2</sub>O and EtOAc. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give the intermediate alcohol as an oil. A solution of the alcohol in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and PBr<sub>3</sub> (1 mL of a 1M solution in CH<sub>2</sub>Cl<sub>2</sub>) was stirred at RT for 30 min. Volatiles were removed in vacuo and the residue was partitioned between aqueous saturated NaHCO<sub>3</sub> and EtOAc. The organic phase was washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give Part A compound (150 mg; 62%) as an oil.

30

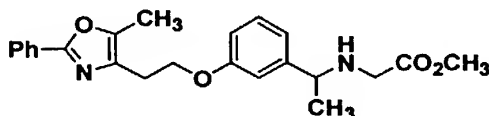


CC1=C(C(=O)O)N(C(=O)Oc2ccc(OCCc3c(C)c(oc3-c4ccccc4)cn4)cc2)C1

A.

CC1=C(CCCOS(=O)(=O)C)C(=N1)C2=CC=CC=C2

B.



To a solution of Part A compound (850 mg, 2.65 mmol) in DCE (15 mL) were successively added glycine methyl ester hydrochloride (333 mg, 2.65 mmol), Et<sub>3</sub>N (554  $\mu$ L, 4.0 mmol), NaBH(OAc)<sub>3</sub> (786 mg; 3.7 mmol) and acetic

15

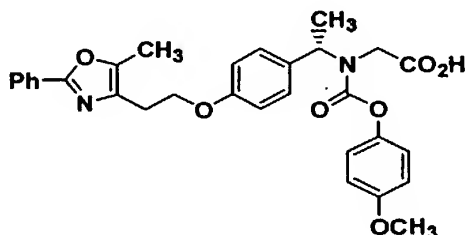
CCOC(=O)N(C)C(=O)Oc1ccc(cc1)OCCc2c(C)c(Oc3ccccc3)n2

25

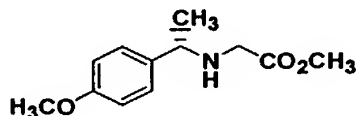
CC1=CC=C(C=C1)OC(=O)N(C)Cc2ccc(OCCc3c(C)c(C4=CC=CC=C4)on3)cc2

5 Volatiles were removed in vacuo and the residue was acidified to pH 2 with aqueous 1 M HCl, then extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The crude product was purified by preparative HPLC (YMC S5 ODS 50 x 10 250 mm column; flow rate = 25 mL/min; continuous 20 min gradient from 70:30 B:A to 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give title compound (28 mg; 72% over 2 steps) as a white solid. [M + H]<sup>+</sup> = 515.3

## 15



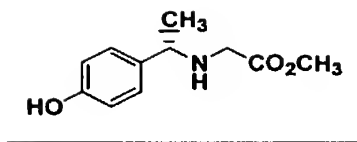
20                      A.



25



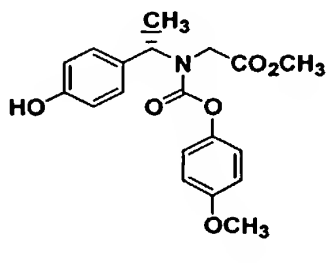
B.



5 To a 0°C solution of the crude Part A compound from  
above in CH<sub>2</sub>Cl<sub>2</sub> (198 mL) was slowly added dropwise BBr<sub>3</sub>  
(12.0 mL; 127 mmol). The reaction was stirred at 0°C for  
3 h, then poured cautiously into a 0°C mixture of  
10 saturated aqueous NH<sub>4</sub>Cl and EtOAc. The aqueous phase was  
neutralized by slow addition of solid NaHCO<sub>3</sub>, then  
extracted with EtOAc (2x). The combined organic extracts  
were washed with brine, dried (MgSO<sub>4</sub>) and concentrated in  
vacuo to furnish Part B compound (7.29 g; 44% over 2  
steps).

15

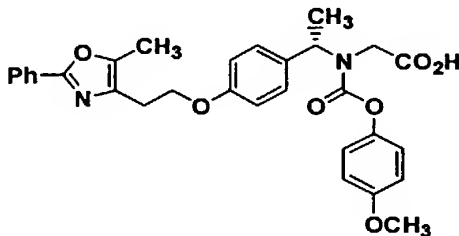
C.



20 To a solution of Part B compound (6.13 g; 29.3  
mmol) in dioxane:H<sub>2</sub>O (98 mL of a 1:1 solution) were  
successively added NaHCO<sub>3</sub> (3.2 g; 38 mmol) and 4-methoxy-  
phenyl chloroformate (3.92 mL; 26.4 mmol). The reaction  
was stirred at RT for 2 h, then partitioned between EtOAc  
25 and H<sub>2</sub>O. The organic phase was washed with brine, dried  
(MgSO<sub>4</sub>), and concentrated in vacuo to give crude Part C  
compound (10.0 g; 95%).

COC1=CC=C(OC(=O)CN(C)Cc2ccc(OCCc3c(C)c(Oc4ccccc4)n3)cc2)C=C1CC1=C(CCCOS(=O)(=O)C)C(=N1)C2=CC=CC=C2

**E.**



To a solution of Part D compound (3.4 g; 6.25 mmol) in THF:H<sub>2</sub>O (31 mL of a 2:1 solution) was added LiOH.H<sub>2</sub>O (0.525 g; 125 mmol). The reaction was stirred at RT overnight for 14 h. EtOAc was added and the solution was acidified with 1 N HCl solution to pH ~2. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow

10

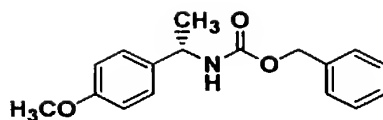
CC1=C(C(=N1)C2=CC=CC=C2)CCOC3=CC=C(C=C3)C[C@H](C)N(C(=O)OCC4=CC=C(OC)C=C4)C5=CC=CC=C5

20  $^1\text{H}$  NMR (DMSO- $\text{d}_6$ ; 400 MHz):  $\delta$  1.50 (2d,  $J = 7.0$  Hz; 3H),  
2.37 (s, 3H), 2.94 (t,  $J = 6.6$  Hz, 2H), 3.74 (s, 3H),  
3.84 (m; 2H), 4.21 (t,  $J = 6.6$  Hz, 2H), 5.35 (m, 1H),  
6.93 (m, 6H), 7.29 (m, 2H), 7.50 (m, 3H), 7.91 (m, 2H)

COc1ccc(cc1)OC(=O)N(C)C[C@H](c2ccc(OCCc3c(C)c(Oc4ccccc4)n3)cc2)C

- 231 -

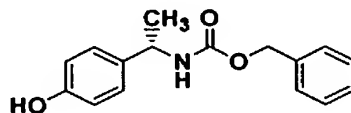
A.



To a RT mixture of (S)-1-(4-methoxyphenyl)-  
5 ethylamine (5.45 g, 36 mmol) in THF (50 mL) and aqueous  
NaHCO<sub>3</sub> (6.05g in 25 mL H<sub>2</sub>O) was added dropwise benzyl  
chloroformate (6.20 mL; 43 mmol). The reaction was  
stirred at RT for 30 min; the organic phase was isolated  
and concentrated in vacuo. The residue was partitioned  
10 between EtOAc and H<sub>2</sub>O (100 mL each); the organic phase was  
washed with brine, dried (MgSO<sub>4</sub>), and concentrated in  
vacuo to about 30 mL volume. An equivalent volume of  
hexane (30 mL) was added and Part A compound (9.12 g;  
89%) crystallized as colorless needles.

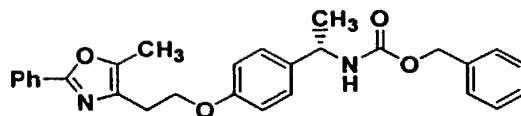
15

B.

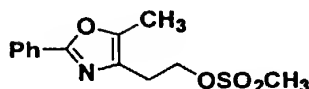


To a -78°C solution of Part A compound (2.50 g; 8.8  
20 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (11 mL) was added dropwise a  
solution of BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (11.4 mL of a 1.0 M solution;  
11.4 mmol) over 25 min. The reaction was allowed to warm  
to 0°C and stirred at 0°C for 6 h, then quenched carefully  
at -78°C by dropwise addition of excess MeOH (6 mL). The  
25 solution was allowed to warm to 0°C and stirred at 0°C for  
5 min. The solution was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (60  
mL) and H<sub>2</sub>O (50 mL). The organic phase was washed  
successively with brine and 5% aqueous NaHCO<sub>3</sub> (50 mL  
each), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The  
30 residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from  
4:1 to 1:1 hex:EtOAc) to furnish Part B compound (1.30 g;  
63% yield based on 650 mg (26%) of recovered unreacted  
Part A compound) as a white solid.

C.

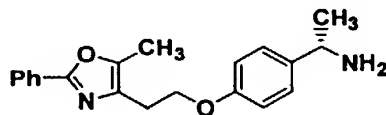


A mixture of Part B compound (1.10 g; 4.1 mmol),  
5  $K_2CO_3$  (680 mg; 4.9 mmol) and the mesylate (1.25 g; 4.4  
mmol)



in MeCN (30 mL) was heated at 90°C for 18 h, then cooled to RT. Volatiles were removed in vacuo, and the residue was partitioned between EtOAc and H<sub>2</sub>O (100 mL each). The organic phase was washed with brine (100 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 9:1 to 3:2 hexane:EtOAc) to give Part C compound (1.40 g; 78%) as a white solid.

D.

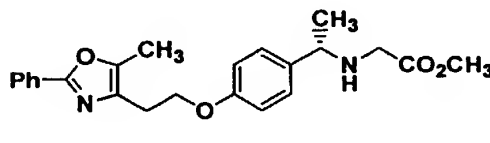


20

A mixture of Part C compound (1.30 g; 2.85 mmol) and 10% palladium on carbon (200 mg) in MeOH (50 mL) was stirred under an atmosphere of H<sub>2</sub> (balloon) at RT for 2 h, at which point the reaction was complete by HPLC. The catalyst was filtered off through Celite<sup>®</sup> and the filtrate was concentrated in vacuo to give Part D compound (600 mg; 65%) as a white solid.

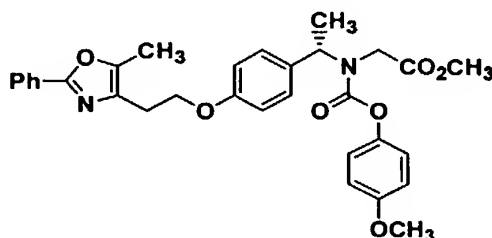
30

**E.**



A solution of Part D compound (600 mg; 1.86 mmol), methyl bromoacetate (230  $\mu$ L; 2.42 mmol) and Et<sub>3</sub>N (337  $\mu$ L; 2.42 mmol) in THF (10 mL) was stirred at RT for 20 h. The reaction mixture was partitioned between H<sub>2</sub>O and EtOAc (60 mL) each. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from hex:EtOAc 4:1 to 1:1) to furnish Part E compound (640 mg; 87%) as an oil.

F.



A solution of Part E compound (600 mg; 1.52 mmol), 4-methoxyphenyl chloroformate (271  $\mu$ L; 1.82 mmol) and DMAP (30 mg; 0.25 mmol) in pyridine (10 mL) was heated at 70°C for 2 h. Since starting material still remained at this point, additional 4-methoxyphenyl chloroformate (271  $\mu$ L; 1.82 mmol) was added and the reaction was heated at 70°C for an additional 1 h. Volatiles were removed in vacuo, and the residue was partitioned between EtOAc (100 mL) and 1M aqueous HCl (60 mL). The organic phase was washed with brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from hex:EtOAc 9:1 to 4:1) to furnish Part F compound (880 mg) as an oil.

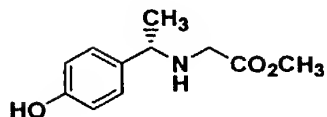
CC1=C(C(=O)N(C1)C(=O)Oc2ccc(OC)cc2)Cc3ccc(OCCc4cnc(C)c4c5ccccc5)cc3

Example 499A

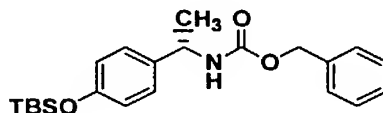
CC1=C(C(=N1)C2=CC=CC=C2)CCOC3=CC=C(C=C3)C(=O)N(C)C(C)C(=O)OC4=CC=C(OC)C=C4

- 235 -

## Alternative Synthesis of Example 498 Part B Compound

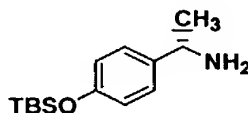


5 A.



A mixture of tert-butyldimethylsilyl chloride (357 mg; 2.36 mmol), (alternative) Example 498A Part B compound from above (535 mg; 1.97 mmol) and imidazole (161 mg; 2.36 mmol) in DMF (5 mL) was stirred at RT for 2 h. The reaction was partitioned between EtOAc (20 mL) and water (50 mL). The organic phase was washed with water (2 x 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 3:1) to give Part A compound (320 mg; 42%) as an oil in addition to recovered starting phenol (150 mg; 20%).

B.

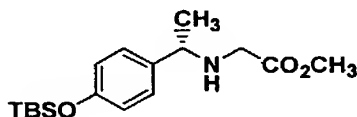


20

A mixture of Part A compound (320 mg; 0.83 mmol) and 10% palladium on carbon (30 mg) in MeOH (30 mL) was stirred under an atmosphere of H<sub>2</sub> (balloon) at RT for 1 h, at which point the reaction was complete by HPLC. The catalyst was filtered off through Celite® and the filtrate was concentrated in vacuo to give Part B compound (230 mg) as a white solid which was used in the next step without further purification.

30

C.

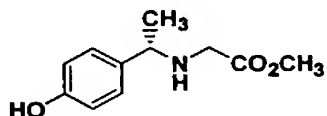




A solution of Part B compound (230 mg), methyl bromoacetate (86  $\mu$ L; 0.91 mmol) and  $\text{Et}_3\text{N}$  (127  $\mu$ L; 0.91 mmol) in THF (10 mL) was stirred at RT for 15h. The reaction mixture was partitioned between  $\text{H}_2\text{O}$  and EtOAc (30 mL) each. The organic phase was washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; stepwise gradient from hex:EtOAc 9:1 to 1:1) to furnish Part C compound (177 mg; 66% over 2 steps) as an oil.

10

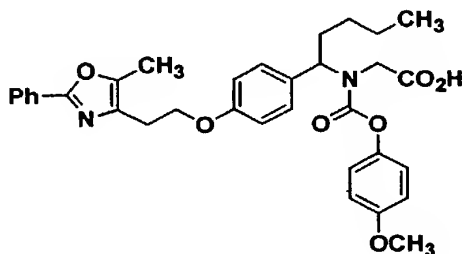
Example 498 Part B Compound



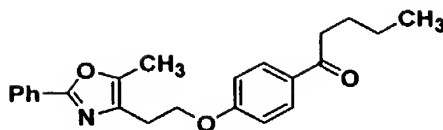
To a solution of Part C compound (177 mg; 0.55 mmol) in THF (5.5 mL) was slowly added tetrabutylammonium fluoride (1.65 mL of a 1 M solution in THF). The reaction was stirred at RT for 10 min, then partitioned between water and EtOAc. The organic phase was washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient from 100%A to 100% B + 10 min hold-time at 100% B, where solvent A = 90:10:0.1  $\text{H}_2\text{O}$ :MeOH:TFA and solvent B = 90:10:0.1 MeOH: $\text{H}_2\text{O}$ :TFA; retention time = 2.6 min) to provide the title compound (97 mg; 84%).

30

Example 500

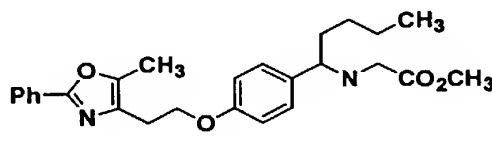


A.



5           A mixture of 4-hydroxyphenyl butyl ketone (2.50 g;  
14.0 mmol), 2-phenyl 5-methyl oxazole-4-ethanol mesylate  
(3.30 g; 11.7 mmol) and  $K_2CO_3$  (1.94 g; 14.0 mmol) in  
acetonitrile (50 mL) was refluxed under Ar for 18 h.  
Volatiles were removed in vacuo and the residue was  
10   partitioned between  $H_2O$  and EtOAc. The aqueous phase was  
extracted with EtOAc. The combined organic extracts were  
washed with aqueous 1M NaOH and  $H_2O$ , dried ( $MgSO_4$ ) and  
concentrated in vacuo. The residue was chromatographed  
( $SiO_2$ ; stepwise gradient from 3:1 to 9:1 hex:EtOAc) to  
15   give Part A compound (3.42 g; 80%) as a white solid.

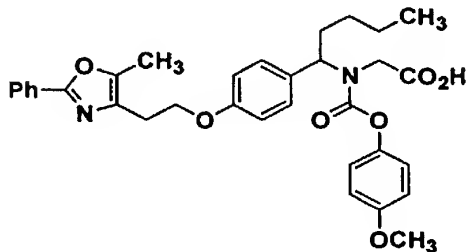
B.



20           A mixture of Part A compound (3.42 g; 9.42 mmol),  
glycine methyl ester HCl salt (1.18 g; 9.42 mmol),  $Et_3N$   
(1.97 mL; 14.1 mmol),  $NaBH(OAc)_3$  (2.80 g; 13.2 mmol) and  
HOAc (0.54 mL; 9.42 mmol) in DCE (20 mL) was stirred at  
25   RT for 6 days. At this point the reaction was  
incomplete, but was not progressing any further. The  
reaction was quenched with saturated aqueous  $NaHCO_3$  (6  
mL), then concentrated in vacuo. The residue was  
partitioned between saturated aqueous  $NaHCO_3$  and EtOAc.  
30   The organic phase was washed with saturated aqueous  $NaHCO_3$ ,  
and  $H_2O$ , then extracted with 1M aqueous HCl (the unreacted  
starting material remained in the organic phase). The  
aqueous phase was basified with NaOH, then extracted with  
EtOAc. The organic phase was washed with  $H_2O$  and brine,

dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give Part B compound (365 mg; 9%) as an oil.

C.

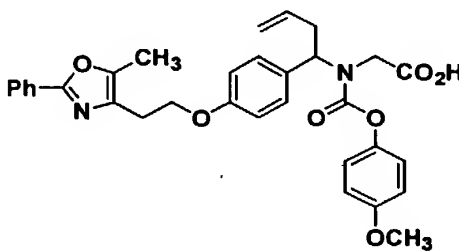


5

To a solution of Part C compound (50 mg; 0.11 mmol) in pyridine (1 mL) was added 4-methoxyphenyl  
10 chloroformate (40  $\mu\text{L}$ ) and DMAP (5 mg). The reaction mixture was heated at  $60^\circ\text{C}$  for 6 h, then was cooled to RT and volatiles were removed in vacuo. The residue was dissolved in THF/MeOH/ $\text{H}_2\text{O}$  (1 mL of a 2:2:1 mixture) and LiOH (30 mg) was added. The reaction was stirred at RT  
15 for 18 h, then was acidified with aqueous 1 M HCl to pH ~ 2. The mixture was extracted with EtOAc (30 mL), washed with  $\text{H}_2\text{O}$  and brine (15 mL each), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give the crude product. This material was purified by preparative HPLC (YMC S5 ODS 30  
20 x 250 mm column; continuous gradient from 60:40 A:B to 100% B over 30 min) to give, after lyophilization from MeOH/ $\text{H}_2\text{O}$ , the title compound (52 mg; 79%) as a white solid.  $[\text{M} + \text{H}]^+ = 573.3$

25

#### Example 501



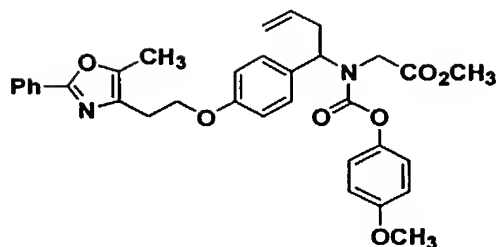
CCOC(=O)CN=Cc1ccc(OCCCC2=C(C)OC(=N2)c3ccccc13)cc1CC1=C(CCOc2ccc(C=O)cc2)C(=N1)c3ccccc3

15

CCOC(=O)CN(C=C)Cc1ccc(OCCc2c(C)c(Oc3ccccc3)n2)cc1

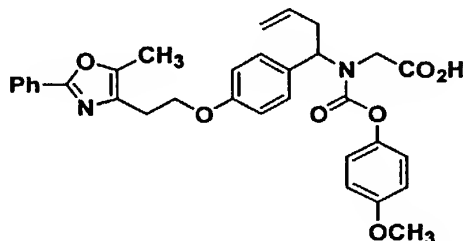
30

C.



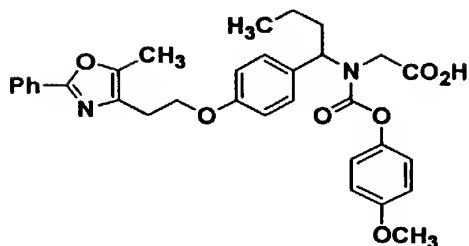
5 To a 0°C solution of Part B compound (150 mg; 0.36 mmol) and Et<sub>3</sub>N (51 µL; 0.36 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added dropwise 4-methoxyphenyl chloroformate (53 µL; 0.36 mmol). The reaction was allowed to warm to RT and stirred at RT for 1 h, then concentrated in vacuo. The  
10 residue was chromatographed (SiO<sub>2</sub>; hexane:EtOAc 2:1) to give Part C compound (200 mg; 98%) as an oil.

D.



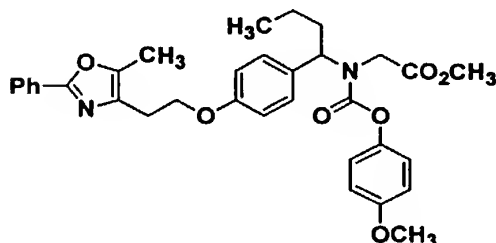
15

A solution of Part C compound (100 mg, 0.18 mmol) and LiOH·H<sub>2</sub>O (30 mg, 0.72 mmol) in THF:MeOH:H<sub>2</sub>O (1 mL of a 1:1:1 solution) was stirred at RT for 2 h. The reaction  
20 mixture was then acidified to pH ~ 2 with aqueous 1N HCl. The aqueous phase was extracted with EtOAc (2x). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo and lyophilized from dioxane to provide title compound (80 mg; 82%) as a white solid.  
25 [M + H]<sup>+</sup> = 557.2

Example 502

5

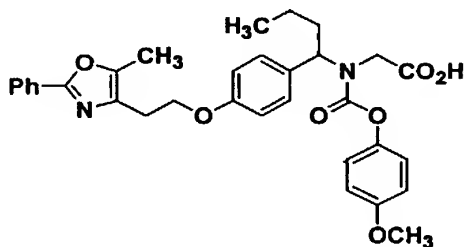
A.



A solution of Example 501 Part C compound (100 mg; 0.18 mmol) in MeOH (10 mL) in the presence of 10% Pd/C (50 mg) was stirred under an H<sub>2</sub> atmosphere for 2 h at RT. The catalyst was then filtered off using a pad of Celite<sup>®</sup>. The filtrate was concentrated in vacuo to give Part A compound (100 mg; 100%) as an oil.

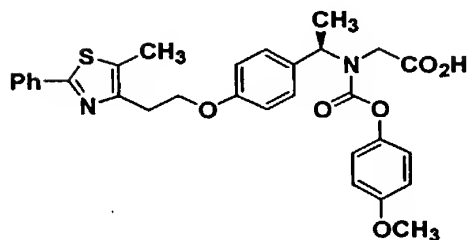
15

B.

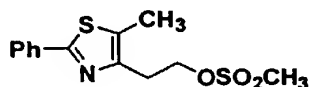


Title compound (87 mg; 90%; white solid lyophilate) was obtained from Part A compound in the same way as Example 501 compound was synthesized from Example 501 Part C compound.  $[M + H]^+ = 559.2$

### Example 503

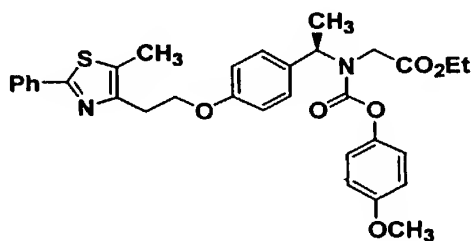


5 A.

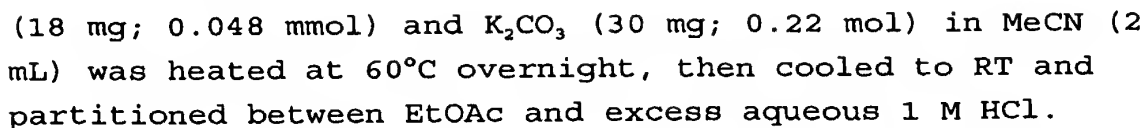


To a solution of 5-methyl 2-phenyl-thiazol-4-yl-ethanol (50 mg; 0.23 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) were successively added  $\text{Et}_3\text{N}$  (50  $\mu\text{L}$ ; 0.36 mmol) and methanesulfonyl chloride (20  $\mu\text{L}$ ; 0.26 mmol). The reaction was stirred at RT for 2 h, then was partitioned between  $\text{CH}_2\text{Cl}_2$  and aqueous 1 M HCl. The organic phase was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo to give Part A compound (68 mg; 100%) as a colorless oil. This material was used in the next step without further purification.

20 B.



25 A mixture of the phenol (prepared using the identical procedures as described for the synthesis of Example 498 Part C compound except that ethyl bromoacetate was used instead of methyl bromoacetate)



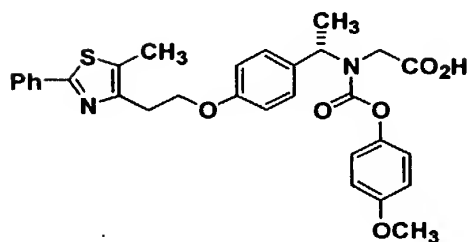
10

CC1=C(C(=N1)C2=CC=CC=C2)CCOC3=CC=C(C=C3)C[C@H](C)N(C(=O)OC4=CC=C(C=C4)OC)C(=O)O

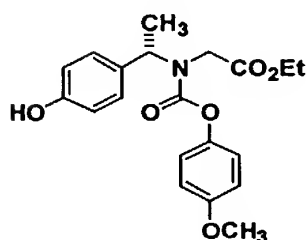
20



### Example 504

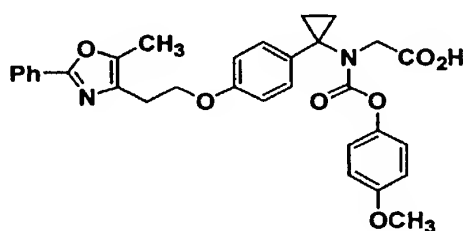


5       The title compound was prepared in exactly the same way as for Example 503 except that the [S]-enantiomer

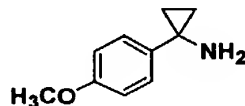


was used for the alkylation step.  $[M + H]^+ = 547.2$

### Example 505



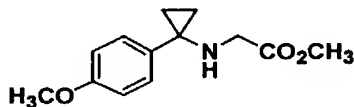
15                      A.



To a solution of 1-(4-methoxyphenyl)-1-cyclopropane-  
20 carboxylic acid (250 mg; 1.3 mmol) in dioxane (8 ml) were  
successively added Et<sub>3</sub>N (198 μL; 1.43 mmol) and diphenyl-  
phosphoryl azide (307 μL; 1.43 mmol). The reaction was  
stirred at RT for 5 min, then heated to 80°C for 3 h.

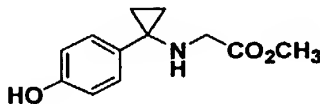
5

15



20

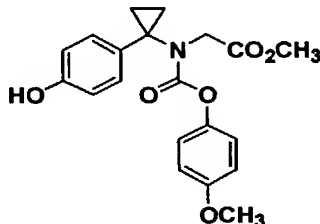
30



m

NH<sub>4</sub>Cl and EtOAc. The organic phase was discarded and the aqueous layer was neutralized by addition of NaHCO<sub>3</sub>, then extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo to give Part C compound (50 mg; 59%).

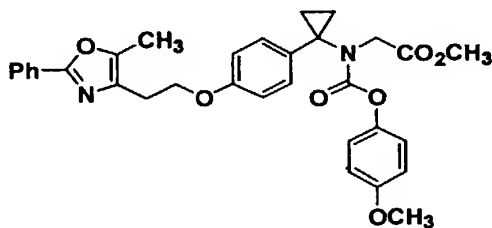
D.



10

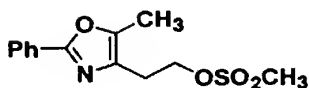
A mixture of Part C compound (50 mg; 0.22 mmol), 4-methoxyphenyl chloroformate (33 mg; 0.22 mol) and NaHCO<sub>3</sub> (25 mg; 0.29 mmol) in 1:1 aqueous dioxane (7.5 mL) was stirred at RT for 2 h. The reaction mixture was partitioned between EtOAc and H<sub>2</sub>O. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part D compound (45 mg; 52%).

E.



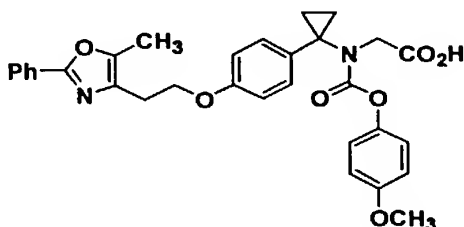
20

A mixture of Part D compound (45 mg; 0.12 mmol), K<sub>2</sub>CO<sub>3</sub> (30 mg; 0.22 mol) and the mesylate (33 mg; 0.12 mmol)



in MeCN (4 mL) was heated at 90°C for 20 h. The reaction was cooled to RT and partitioned between EtOAc and H<sub>2</sub>O. The aqueous phase was extracted with EtOAc (2x); the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 9:1 to 1:1 hex:EtOAc) to provide Part E compound (42 mg; 65%).

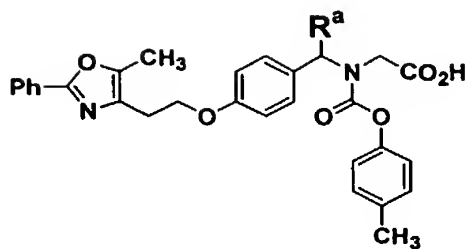
F.



10

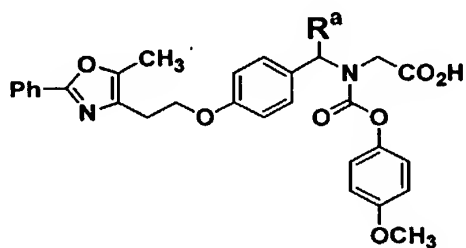
A solution of Part E compound (42 mg; 0.08 mmol) and LiOH.H<sub>2</sub>O (6 mg; 0.15 mmol) in 2:1 THF:H<sub>2</sub>O (3.8 mL) was stirred at RT overnight. The reaction mixture was acidified to pH 2 with excess aqueous 1 M HCl and extracted with EtOAc (2x). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo; the residue was purified by preparative HPLC (as described for Example 498) to give the title compound (28 mg; 68%) as a colorless oil. [M + H]<sup>+</sup> = 543.2

Following procedures as described above, the Examples 506 to 518 compounds were prepared.

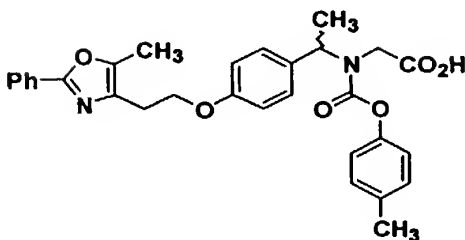


Example No.	R <sup>a</sup>	[M+H] <sup>+</sup>
506	(±) -Me	515.3
507	(±) n-Bu	557.4

5



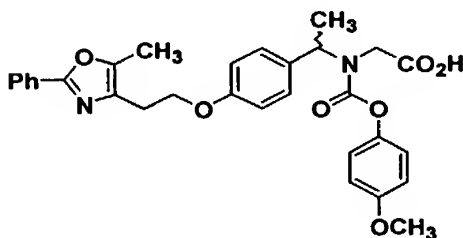
Example No.	R <sup>a</sup>	[M+H] <sup>+</sup>
508	(±) Me	531.3
509	(±) Et	545.1
510	(±) i-Bu	573.3
511	(±)	571.3

Example 506

5

$^1\text{H}$  NMR (DMSO- $d_6$ ; 400 MHz):  $\delta$  1.47 and 1.54 (2d,  $J$  = 7.5 Hz; 3H), 2.29 (s, 3H), 2.37 (s, 3H), 2.93 (t,  $J$  = 6.6 Hz, 2H), 3.81 (2d,  $J$  = 18 Hz; 2H), 4.21 (t,  $J$  = 6.6 Hz, 2H), 5.3 (m, 1H), 6.94 (m, 4H), 7.18 (d,  $J$  = 8.4 Hz, 2H), 7.31 (m, 2H), 7.49 (m, 2H)

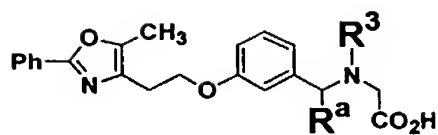
10

Example 508

15

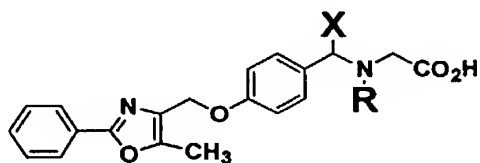
$^1\text{H}$  NMR (DMSO- $d_6$ ; 400 MHz):  $\delta$  1.47 and 1.54 (2d,  $J$  = 7.5 Hz; 3H), 2.37 (s, 3H), 2.94 (t,  $J$  = 6.6 Hz, 2H), 3.74 (s, 3H), 3.81 (m, 2H), 4.21 (t,  $J$  = 6.6 Hz, 2H), 5.36 (m, 1H), 6.94 (m, 4H), 7.29 (m, 2H), 7.49 (m, 3H), 7.91 (m, 2H)

20

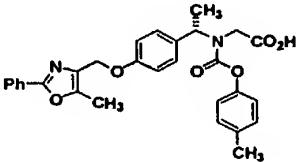
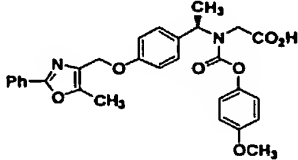
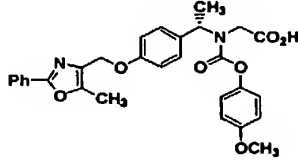


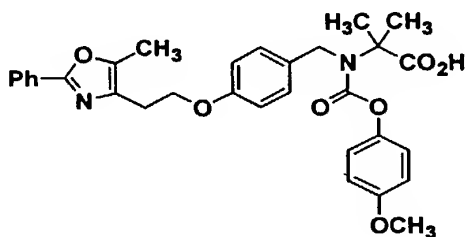
Example No.	Structure	[M+H] <sup>+</sup>
512	 (±)	531.3

5 The synthesis of Examples 513-518 involved the use of Example 541 Part B compound as the alkylating agent.



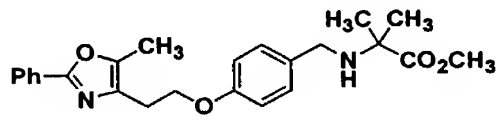
Example No.	Structure	[M+H] <sup>+</sup>
513	 (±)	517.2
514	 (±)	517.2
515	 (±)	501.2

Example No.	Structure	[M+H] <sup>+</sup>
516		501.2
517		517.2
518		517.2

Example 519

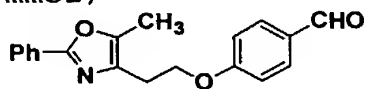
5

A.



10

A mixture of methyl  $\alpha$ -aminoisobutyrate hydrochloride (108 mg; 0.7 mmol), Et<sub>3</sub>N (146  $\mu$ L; 1.1 mmol), NaBH(OAc)<sub>3</sub> (222 mg; 1.1 mmol) and the aldehyde (215 mg; 0.7 mmol)

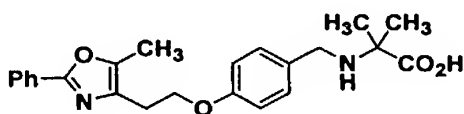


15



in DCE (5 mL) was stirred at RT for 21 h. Some starting material remained, so the reaction was heated at 55°C for 4 h (no further reaction). Saturated aqueous NaHCO<sub>3</sub> was added, and volatiles were removed in vacuo. The residue was partitioned between H<sub>2</sub>O and EtOAc. The aqueous phase was extracted with EtOAc (2x). The combined organic extracts were washed with brine and extracted with aqueous 1 M HCl. The aqueous phase was basified with solid NaOH and extracted with EtOAc (2x). The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give crude Part A compound (174 mg; 61%).

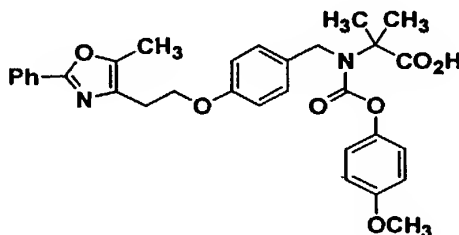
B.



15

A solution of Part A compound (120 mg; 0.29 mmol) aqueous LiOH (2.0 mL of a 0.3 M solution of a 1:1:1 mixture of THF:MeOH:H<sub>2</sub>O) was stirred at RT overnight. The reaction was acidified to pH ~ 2 with aqueous 1 M HCl, then was concentrated in vacuo and purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 mL/min; continuous gradient from 40:60 B:A to 100% B over 30 min, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to furnish Part B compound (60 mg; 53%) as a syrup.

C.

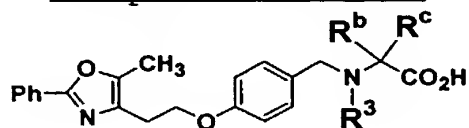


30

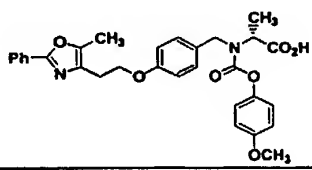
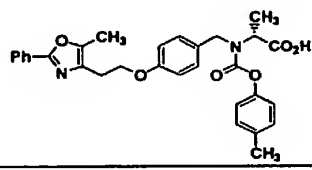
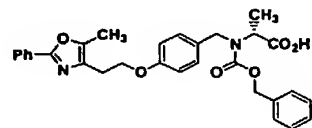
A solution of Part B compound (25 mg; 0.06 mmol), 4-methoxyphenyl chloroformate (20  $\mu$ L) in pyridine (1 mL) was heated at 60°C for 6 h. Volatiles were removed in vacuo and the residue was partitioned between EtOAc (2 mL) and aqueous 1 M HCl (1 mL). The organic phase was concentrated in vacuo and the residue was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 mL/min; continuous gradient from 40:60 B:A to 100% B over 20 min, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA; solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to furnish title compound (4 mg; 12%) as a white foam.  $[M + H]^+ = 545.3$

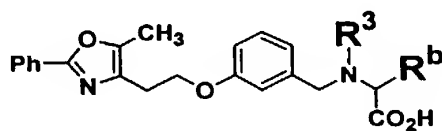
Following the procedures as set out hereinbefore, the following Examples 520 to 535 compounds were prepared.

Examples 520 to 535

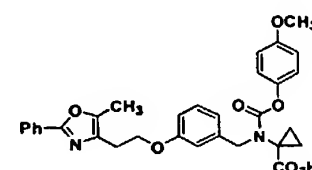
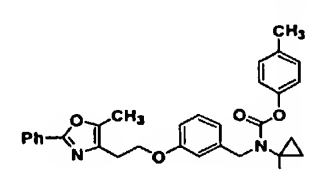


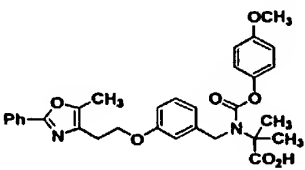
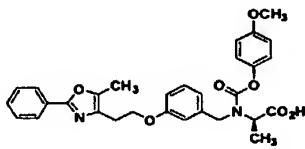
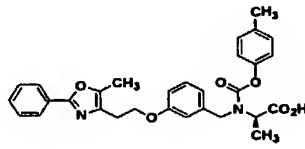
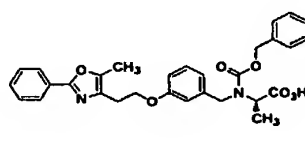
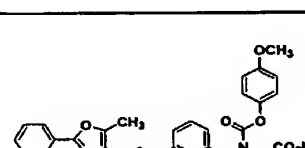
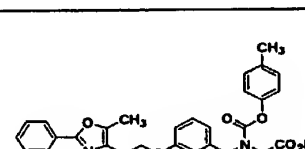
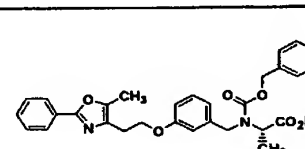
Example No.	Structure	$[M+H]^+$
520		543.4
521		527.3
522		531.2
523		515.2

Example No.	Structure	[M+H] <sup>+</sup>
524		531.2
525		515.2
526		515.2



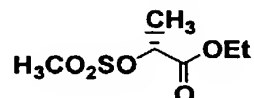
5

Example No.	Structure	[M+H] <sup>+</sup>
527		543.3
528		527.3

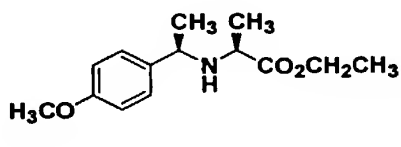
529		545.3
530		531.2
531		515.2
532		515.2
533		531.2
534		515.2
535		515.2

CC1=C(C(=C(C=C1)COC2=CC=CC=C2C(=O)N(C)C(C)C(=O)O)C3=CC=CC=C3)C(=N4C(=C(C=C4)C)O5C=CC=C(C=C5)C6=CC=CC=C6)O

A.



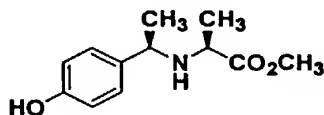
20 B.



- 257 -

vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; stepwise gradient from 99:1 to 97:3  $\text{CHCl}_3$ :MeOH) to give Part B compound (330 mg; 70%) as an oil.

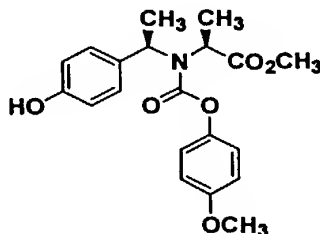
5 C.



To a  $0^\circ\text{C}$  solution of Part B compound (330 mg; 1.39 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was slowly added dropwise  $\text{BBr}_3$  (3.0 mL of a 1 M solution in  $\text{CH}_2\text{Cl}_2$ ; 30 mmol). The reaction was stirred at  $10^\circ\text{C}$  for 3 h, then quenched by cautious addition of saturated aqueous  $\text{NH}_4\text{Cl}$  and  $\text{CH}_2\text{Cl}_2$ . The isolated aqueous phase was neutralized by slow addition of solid  $\text{NaHCO}_3$ , then extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to furnish crude Part C compound (150 mg; 48%), which was used in the next reaction without further purification.

20

D.

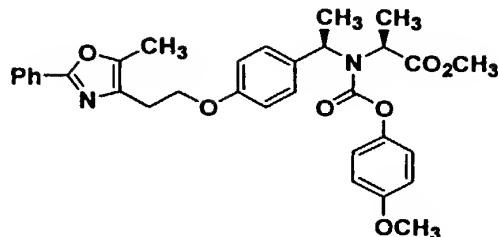


To a solution of Part C compound (300 mg; 1.35 mmol) in dioxane: $\text{H}_2\text{O}$  (6 mL of a 1:1 solution) were successively added  $\text{NaHCO}_3$  (500 mg; 5.95 mmol) and 4-methoxyphenyl chloroformate (300  $\mu\text{L}$ ; 2.0 mmol) slowly. The reaction was stirred at RT for 1 h, then partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic phase was washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated in vacuo to give a crude residue, which was chromatographed ( $\text{SiO}_2$ ; stepwise

30

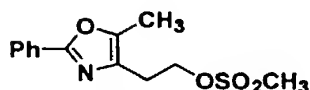
gradient from 3:1 to 1:1 hexane:EtOAc) to furnish Part D compound (330 mg; 66%).

E.



5

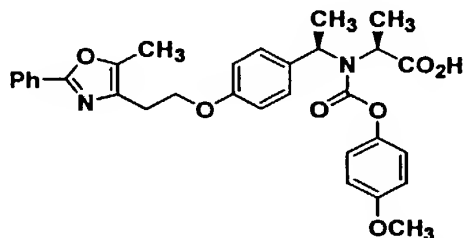
To a solution of Part D compound (330 mg; 0.88 mmol) in MeCN (20 mL) were successively added  $K_2CO_3$  (165 mg; 1.2 mmol) and the mesylate (337 mg; 1.2 mmol).



The reaction mixture was heated at 95°C for 16 h, then cooled to RT and filtered. The filtrate was concentrated in vacuo and then partitioned between EtOAc and  $H_2O$ . The organic phase was washed with brine, dried ( $MgSO_4$ ) and concentrated in vacuo. The residue was chromatographed ( $SiO_2$ ; 3:1 hexane:EtOAc) to give Part E compound (350 mg; 71%).

20

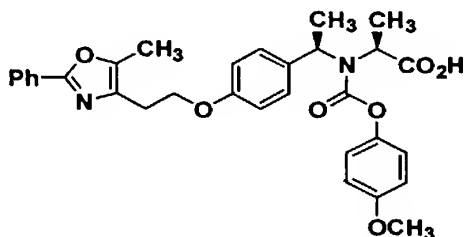
F.



To a solution of Part E compound (350 mg; 0.62 mmol) in THF: $H_2O$  (15 mL of a 2:1 solution) was added  $LiOH \cdot H_2O$  (52 mg; 1.2 mmol). The reaction was stirred at RT overnight for 14 h; then EtOAc was added and the

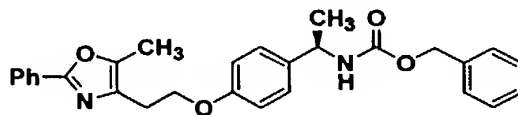
- solution acidified with 1 N HCl solution to pH ~ 2. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate = 25 mL/min; 20 min continuous gradient from 50:50 B:A to 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA; retention time = 26 min) and lyophilized from dioxane to give the title compound (208 mg; 61% yield) as a white solid.
- 10 [M + H]<sup>+</sup> = 545.3

Alternative Synthesis of Example 536:

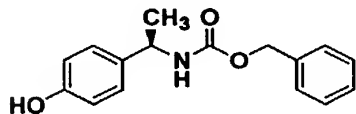


15

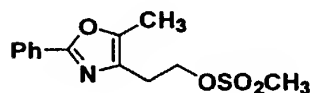
A.



- A mixture of the phenol [500 mg; 1.94 mmol; prepared from (R)-1-(4-methoxyphenyl)ethylamine as for the alternative synthesis of Example 498],
- 20



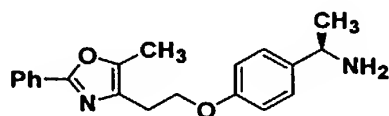
- 25 K<sub>2</sub>CO<sub>3</sub> (400 mg; 2.89 mmol) and the mesylate (710 mg; 2.52 mmol)





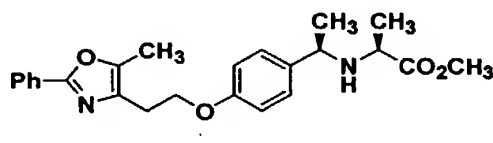
5

10

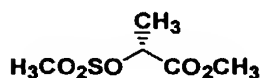


15

C.



25

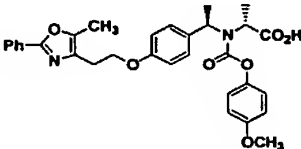
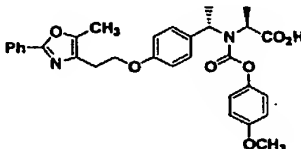
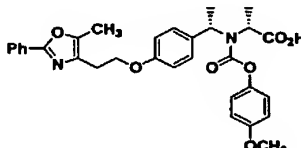


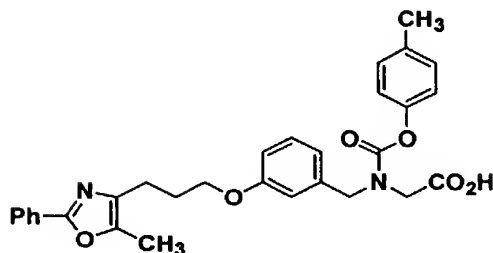
30

filtrate was concentrated in vacuo, and the residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from hex:EtOAc 3:1 to 1:1) to furnish Part C compound (98 mg; 47%) as an oil. This intermediate was then used for the preparation of Example 536 in an identical manner to that previously shown.

Examples 537 to 539

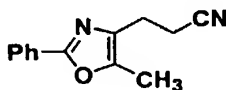
10 Following the procedures set out hereinbefore, the Examples 537 to 539 compounds were prepared.

Example No.	Structure	[M+H] <sup>+</sup>
537		545.3
538		545.3
539		545.3

Example 540

5

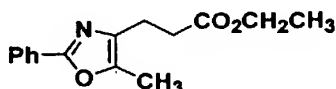
A.



10 To a 0°C solution of 5-methyl-2-phenyl-oxazol-4-yl  
ethanol (5.0 g; 24.6 mmol), acetone cyanohydrin (3.35 mL;  
36.9 mmol) and Ph<sub>3</sub>P (7.5 g; 29.5 mmol) in THF (60 mL) was  
added DEAD (6.0 mL; 36.9 mmol) dropwise. After addition  
was complete, the reaction mixture was warmed to RT and  
15 stirred overnight at RT. Volatiles were removed in  
vacuo, and the residue was chromatographed (SiO<sub>2</sub>;  
hexane:EtOAc 2:1) to give Part A compound (4.5 g; 86%) as  
an oil.

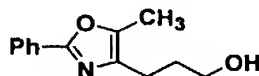
20

B.

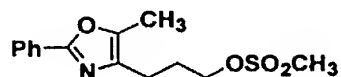


25 A solution of Part A compound (4.5 g; 21.2 mmol)  
and H<sub>2</sub>SO<sub>4</sub> (concentrated; 20 mL) in EtOH (100 mL) was  
heated under reflux overnight. The solution was  
concentrated in vacuo to 1/3 its original volume, then  
EtOAc (150 mL) and H<sub>2</sub>O (100 mL) were cautiously added.  
The organic phase was washed with saturated aqueous NaHCO<sub>3</sub>,  
30 (2 x 100 mL) and brine (150 mL), dried (MgSO<sub>4</sub>), and  
concentrated in vacuo to give a crude oil. This material

c.

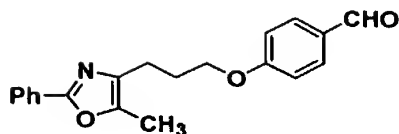


D.



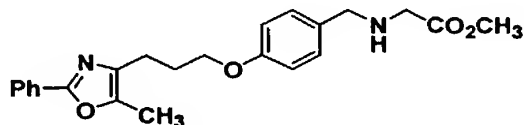
- 264 -

E.



A mixture of Part D compound (380 mg; 1.29 mmol),  
5 4-hydroxybenzaldehyde (188 mg; 1.55 mmol) and  $K_2CO_3$  (214  
mg; 1.55 mg) in MeCN (12 mL) was refluxed in an oil bath  
for 17 h. At this point all starting Part D compound had  
been consumed (but there was a significant quantity of  
the hydrolysis by-product, Part C compound) by HPLC/MS.  
10 The reaction was cooled to RT and the solid precipitates  
were filtered off. The filtrate was concentrated in  
vacuo and partitioned between EtOAc (60 mL) and  $H_2O$  (40  
mL). The organic phase was washed with brine (40 mL),  
dried ( $MgSO_4$ ), and concentrated in vacuo to give the crude  
15 product. This material was chromatographed ( $SiO_2$ ;  
stepwise gradient from 4:1 to 1:2 hex:EtOAc) to give Part  
E compound (150 mg; 36%) as an oil in addition to Part C  
compound (100 mg; 36%).

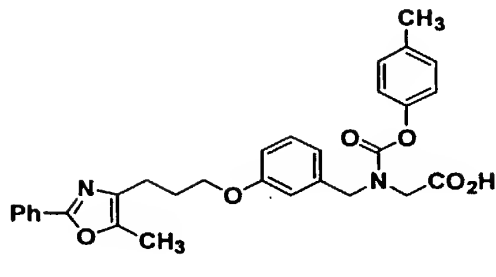
20 F.



A mixture of Part E compound (150 mg; 0.50 mmol),  
25 glycine methyl ester hydrochloride (75 mg; 0.60 mmol) and  
 $Et_3N$  (84  $\mu L$ ; 0.60 mmol) in MeOH (5 mL) was stirred at RT  
for 6 h, after which  $NaBH_4$  (50 mg) was added cautiously  
portionwise. The reaction mixture was stirred at RT  
overnight, after which volatiles were removed in vacuo.  
30 The residue was partitioned between EtOAc and  $H_2O$ . The  
organic phase was washed with brine, dried ( $Na_2SO_4$ ) and

concentrated in vacuo to give Part F compound (180 mg; 97%) as an oil.

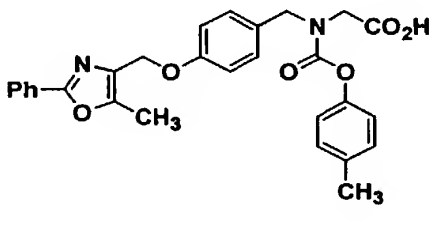
G.



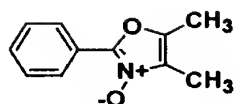
A mixture of Part F compound (23 mg; 0.060 mmol), Et<sub>3</sub>N (10  $\mu$ L; 0.66 mmol) and 4-tolyl chloroformate (10  $\mu$ L; 0.066 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at RT for 2 h. Volatiles were removed in vacuo and the residue was dissolved in a solution of THF/MeOH/H<sub>2</sub>O (1 mL of a 2:2:1 mixture); LiOH.H<sub>2</sub>O (14 mg; 0.33 mmol) was added, and the reaction was stirred at RT for 2 h. Volatiles were removed in vacuo, and the residue was partitioned between aqueous 1 M HCl and EtOAc. The organic extract was concentrated in vacuo and the residue was purified by preparative HPLC (YMC ODS S5 30 mm x 250 mm column, continuous 25 minute gradient from 40% B:60% A to 100% B, hold at 100% B for 15 min, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA; flow rate = 25 mL/min) to give the title compound as a white solid (13 mg; 45% over 2 steps). [M + H]<sup>+</sup> = 515.3

25

### Example 541

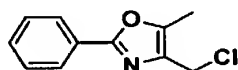


A.



5 To a solution of benzaldehyde (23.8 g, 234 mmol) in EtOAc (150 mL; pre-saturated with HCl gas) was added 2,3-butanedione mono-oxime (25.0 g, 234 mmol) in one portion and the resulting solution was stirred at RT for 12 h. Analytical HPLC indicated that all starting materials had  
10 been consumed. The reaction mixture was concentrated in vacuo to yield Part A compound as a white solid, which was used in the next step without further purification.

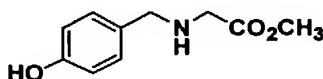
B.



15

To a solution of Part A compound in  $\text{CHCl}_3$  (200 mL) was added dropwise  $\text{POCl}_3$  (30 mL, 320 mmol). The reaction  
20 was stirred for 12 h at  $50^\circ\text{C}$ , then was concentrated in vacuo. The brown residue was partitioned between EtOAc (300 mL) and 1N aqueous NaOH. The organic phase was washed with brine, dried, ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ;  $\text{Et}_2\text{O}$ ) to  
25 give Part B compound (41.5 g; 86%) as a light brown solid (>95% pure by analytical HPLC and  $^1\text{H}$ -NMR analysis).

C.

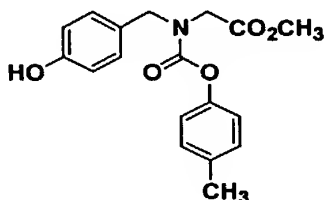


30

A solution of 4-hydroxybenzaldehyde (20 g, 160 mmol), glycine methyl ester hydrochloride (22 g, 180 mmol) and  $\text{Et}_3\text{N}$  (25 mL, 180 mmol) in MeOH (200 mL) was  
35 stirred at RT for 12 h. The reaction mixture was cooled to  $0^\circ\text{C}$  and  $\text{NaBH}_4$  (9.0 g, 240 mmol) was added portionwise

while maintaining the reaction temperature at <RT. The reaction mixture was stirred for 5 h, then was concentrated in vacuo to give crude Part C compound, which was used in the next step without further purification.

D.

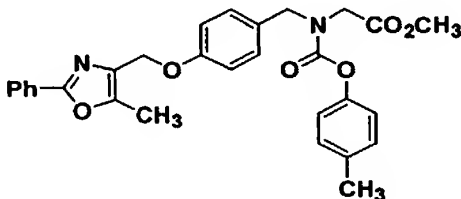


10

To a solution of crude Part C compound in Et<sub>2</sub>O (300 mL) and H<sub>2</sub>O (200 mL) were added NaHCO<sub>3</sub> (20 g, 240 mmol, in a single portion) and 4-tolyl chloroformate (15 mL, 150 mmol; dropwise). The biphasic reaction mixture was stirred for 12 h at RT. The aqueous phase was then extracted with Et<sub>2</sub>O (2 x 200 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 3:1 to 1:1 hexane:EtOAc) to give Part D compound (40.8 g; 76% over 2 steps) as an oil.

20

E.



25

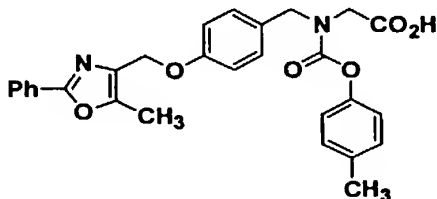
A solution of Part B compound (14.5 g, 70 mmol), Part C compound (21.6 g, 67 mmol) and K<sub>2</sub>CO<sub>3</sub> (18.4 g, 134 mmol) in CH<sub>3</sub>CN (150 mL) was stirred at 80°C for 12 h. The reaction was cooled to RT and volatiles were removed in vacuo. The brown oily residue was partitioned between

30



EtOAc (250 mL) and brine (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; stepwise gradient from 3:1 to 1:1 hexane:EtOAc) to give Part D compound (23.6 g; 71%) as a colorless oil.

F.

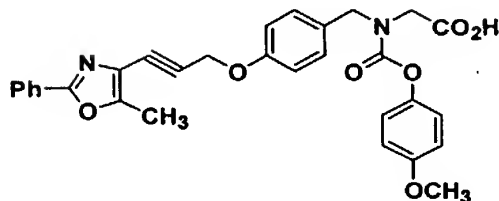


10

A solution of Part D compound (23.6 g, 47.4 mmol) and  $\text{LiOH}\cdot\text{H}_2\text{O}$  (4.0 g, 95 mmol) in THF (200 mL) and  $\text{H}_2\text{O}$  (120 mL) was stirred at RT for 4 h. The reaction mixture was then acidified to pH ~ 2 with aqueous 1N HCl. The aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to yield an oily residue, which was recrystallized from EtOAc to provide title compound (19.4 g; 84%) as a white solid.  $[\text{M} + \text{H}]^+ = 487.23$ ;

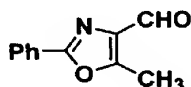
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ; 400 MHz):  $\delta$  2.32 (s, 3H), 2.46 (s, 3H), 3.99 & 4.04 (2s, 2H), 4.47 & 4.54 (2s, 2H), 5.01 and 5.00 (2s, 2H), 6.99 (d,  $J = 8.4$  Hz, 2H), 7.05 (m, 2H), 7.17 (d,  $J = 8.4$  Hz, 2H), 7.31 (m, 2H); 7.49 (m, 3H), 8.01 (m, 2H);

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ; 400 MHz):  $\delta$  2.31 (s, 3H), 2.44 (s, 3H), 4.00 (s, 2H), 4.55 (2s, 2H), 5.00 (2s, 2H); 6.99 (m, 4H); 7.13 (m, 2H), 7.21 (d,  $J = 8.8$  Hz, 2H); 7.31 (m, 2H); 7.44 (s, 3H); 8.01 (s, 2H)

Example 542

5

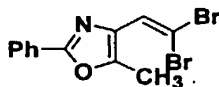
A.



10 A mixture of 2-phenyl-5-methyl-oxazole-4-acetic acid (470 mg; 2.17 mmol; Maybridge) pyridine N-oxide (830 mg; 8.74 mmol) and acetic anhydride (350 mg; 3.57 mmol) in toluene (10 mL) was heated at 90°C for 12 h, then concentrated in vacuo. The residue was then partitioned between EtOAc and 1M aqueous HCl. The organic phase was washed with saturated aqueous NaHCO<sub>3</sub>, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give a dark brown oil. This material was chromatographed (SiO<sub>2</sub>; 4:1 hex:EtOAc) to give Part A compound (143 mg; 35%) as an oil.

20

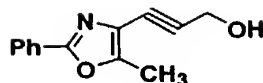
B.



25 To a 0°C solution of Part A compound (600 mg; 3.21 mmol) and Ph<sub>3</sub>P (3.37 g; 12.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added dropwise a solution of CBr<sub>4</sub> (2.13 g; 6.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The solution was stirred at 0°C for 2 h, then allowed to warm to RT and stirred at RT overnight.

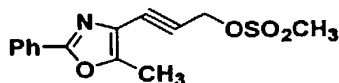
30 Volatiles were removed in vacuo and the residue was chromatographed (85:15 hexane:EtOAc) to furnish Part B compound (1.08 g; 98%) as a pale yellow solid.

C.



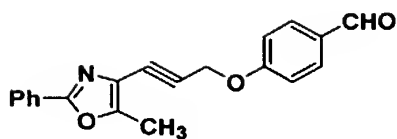
5 To a  $-78^{\circ}\text{C}$  solution of Part B compound (1.12 g; 3.26 mmol) in THF (60 mL) was added n-butyllithium dropwise (4.2 mL of a 1.6 M solution in hexane; 6.72 mmol) over 25 min, while maintaining the internal temperature at  $\leq -71^{\circ}\text{C}$ . The reaction was stirred at  $-78^{\circ}\text{C}$  for 1 h, then allowed to warm slowly to  $0^{\circ}\text{C}$ . Paraformaldehyde (305 g) was then added in one portion and the reaction was stirred at  $0^{\circ}\text{C}$  for 3 h and then quenched with saturated aqueous  $\text{NH}_4\text{Cl}$ . The aqueous phase was extracted with EtOAc (2x); the combined organic  
10 extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give a dark oil. This material was chromatographed ( $\text{SiO}_2$ ; 3:2 hex:EtOAc) to give Part C compound (466 mg; 67%) as a yellow solid.

20 D.



To a  $0^{\circ}\text{C}$  solution of Part C compound (466 mg; 2.19 mmol) and  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$  was added dropwise methanesulfonyl chloride (190  $\mu\text{L}$ ; 2.45 mmol) and the reaction was stirred at  $0^{\circ}\text{C}$  for 1 h. The mixture was then partitioned between  $\text{CH}_2\text{Cl}_2$  and cold 1M aqueous  $\text{HCl}$ . The organic phase was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The crude product was  
30 chromatographed ( $\text{SiO}_2$ ; 3:2 hex:EtOAc) to give Part D compound (533 mg; 84%) as an off-white solid.

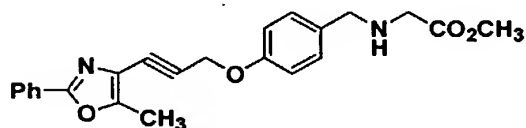
E.



5 A mixture of Part D compound (198 mg; 0.68 mmol),  
4-hydroxybenzaldehyde (96 mg; 0.79 mmol) and  $K_2CO_3$  (141  
mg; 1.02 mmol) in  $CH_3CN$  (13 mL) was heated at  $70^\circ C$  for  
3 h, then stirred at RT overnight. Volatiles were  
10 removed in vacuo, and the residue was partitioned between  
EtOAc and 1 M aqueous NaOH. The organic phase was washed  
with brine, dried ( $Na_2SO_4$ ) and concentrated in vacuo to  
give crude Part E compound (190 mg; 88%) as a yellow oil,  
which was used in the next step without further  
purification.

15

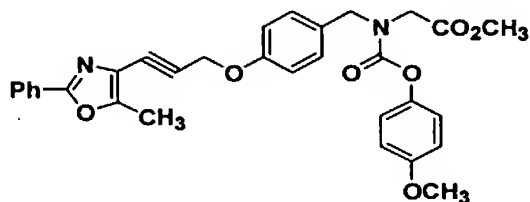
F.



20 A mixture of Part E compound (123 mg; 0.39 mmol),  
glycine methyl ester hydrochloride (248 mg; 1.98 mmol)  
and  $Et_3N$  (600  $\mu L$ ; 4.3 mmol) in DCE (15 mL) was stirred at  
RT for 15 min, after which  $NaBH(OAc)_3H$  (262 mg; 1.2 mmol)  
was added in one portion. The reaction was stirred for  
25 16 h at RT, after which additional  $NaBH(OAc)_3H$  (200 mg;  
0.94 mmol) was added. Stirring was continued for 3 h,  
after which still more  $NaBH(OAc)_3H$  (200 mg; 0.94 mmol) was  
added. The reaction was stirred at RT for 48 h, after  
which all Part E compound had been consumed. The  
30 reaction mixture was partitioned between  $CH_2Cl_2$  and  
aqueous  $NaHCO_3$ . The aqueous phase was extracted with  
 $CH_2Cl_2$  (2x). The combined organic extracts were washed  
with brine, dried ( $Na_2SO_4$ ) and concentrated in vacuo. The  
crude product was chromatographed ( $SiO_2$ ; stepwise gradient

from 1:1 to 2:3 hex:EtOAc) to give Part F compound (120 mg; 79%) as a colorless oil which solidified on standing.

G.

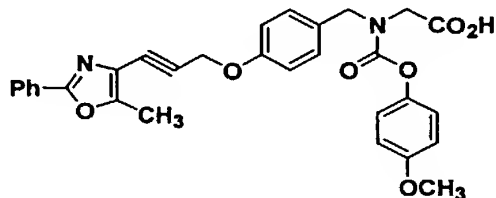


5

To a solution of Part F compound (180 mg; 0.46 mmol) and pyridine (100  $\mu$ L; 1.24 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added 4-methoxyphenyl chloroformate (105  $\mu$ L; 0.71 mmol). The reaction was stirred at RT for 3.5 h, then partitioned between aqueous  $\text{NaHCO}_3$  and EtOAc. The aqueous phase was extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The crude product was chromatographed ( $\text{SiO}_2$ ; hex:EtOAc 3:2) to give Part G compound (232 mg; 93%) as a colorless oil.

15

H.



20

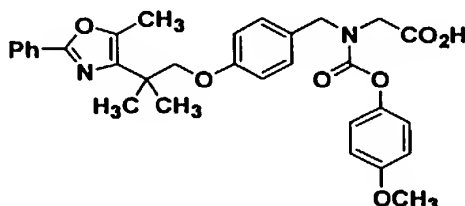
To a solution of Part G compound (232 mg; 0.43 mmol) in THF: $\text{H}_2\text{O}$  (12 mL of a 5:1 mixture) was added  $\text{LiOH}\cdot\text{H}_2\text{O}$  (1.3 mmol). The solution was stirred at RT overnight, then acidified with aqueous 1M HCl and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The crude product was purified by preparative HPLC (YMC S5 ODS 30 x 75 mm column, flow rate = 20 mL/min; continuous gradient from 70:30 B:A to 100% B,

30

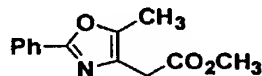
where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give title compound (160 mg; 71%) as a white solid. [M + H]<sup>+</sup> = 527.2

5

### Example 543

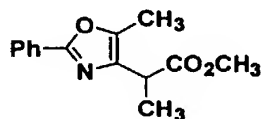


A.



A solution of 5-methyl-2-phenyloxazole-4-yl-acetic acid (4.0 g; 18 mmol) and concentrated HCl (2 mL) in MeOH (60 mL) was heated at reflux overnight. Volatiles were removed in vacuo; the residue was partitioned between H<sub>2</sub>O and EtOAc. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude Part A compound as a colorless oil (4.00 g; 94%) which was used in the next step without further purification.

B.



25

To a -78°C solution of LDA (15.0 mL of a 2.0 M solution in heptane/THF; 30 mmol; Aldrich) were successively added dropwise a solution of Part A compound (2.3 g; 10 mmol) in THF (6 mL) and HMPA (500 µL; 2.9 mmol). The solution was stirred at -78°C for 30 min, after which methyl iodide (1.87 mL; 30 mmol) was added dropwise. The solution was stirred at -78°C for 1 h,

5

10



15

20

25

30

D.



10

15

20

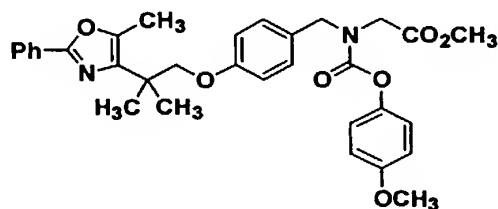
30

35



in vacuo. The residue was partitioned between H<sub>2</sub>O and EtOAc. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give crude Part F compound (300 mg; 98%) which was used in the next  
5 reaction without further purification.

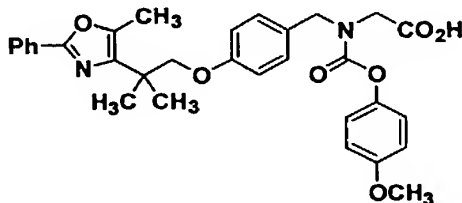
G.



10

To a 0°C solution of Part F compound (150 mg; 0.37 mmol) and Et<sub>3</sub>N (51 µL; 0.37 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added 4-methoxyphenyl chloroformate (55 µL; 0.37 mmol). The reaction was allowed to warm to RT and stirred at RT  
15 for 2 h. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; 5:1 hexane:EtOAc) to furnish Part G compound (130 mg; 63%).

H.

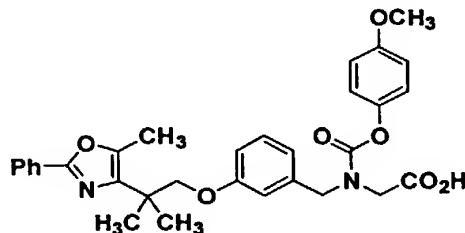


20

A solution of Part G compound (130 mg) and LiOH.H<sub>2</sub>O (39 mg) in H<sub>2</sub>O/THF/MeOH (2 mL of a 1:2:2 mixture) was stirred at RT for 2 h. Volatiles were removed in vacuo,  
25 and the residue was acidified with 1.0 M aqueous HCl, then extracted with EtOAc. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give a residue, which was purified by preparative HPLC (YMC S5 ODS  
30 reverse phase C18, 30 x 250 mm column; flow rate = 25

5 lyophilate.  $[M + H]^+ = 545.4$

### Example 544

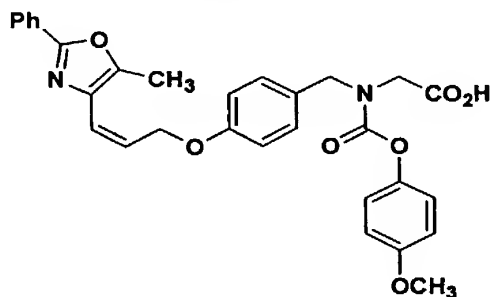


10

Title compound was prepared in analogous fashion to Example 543 except that 3-hydroxybenzaldehyde was used instead of 4-hydroxybenzaldehyde (in the preparation of Example 543 Part E compound).  $[M + H]^+ = 545.4$

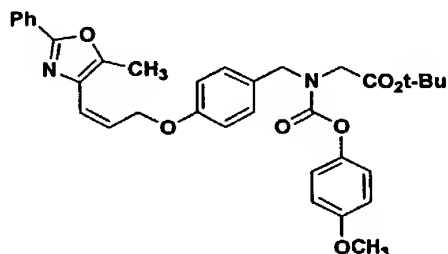
15

### Example 545

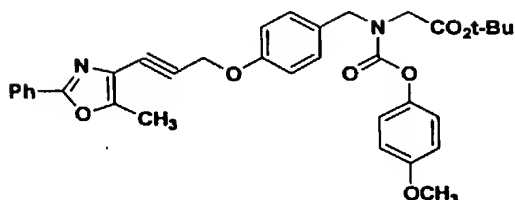


20

A.



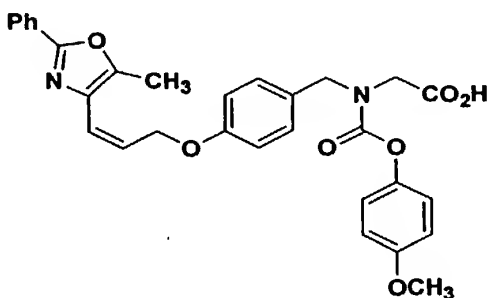
A mixture of the acetylene (38 mg; 0.065 mmol)



(synthesized in a completely analogous fashion to Example  
5 542 Part G compound with glycine tert-butyl ester  
hydrochloride instead of glycine methyl ester  
hydrochloride), quinoline (80 mg; 0.62 mmol) and  
Lindlar's catalyst (8 mg; Pd/CaCO<sub>3</sub>; Aldrich) in MeOH (8  
mL) was stirred under an atmosphere of H<sub>2</sub> at 0°C for 20  
10 min. Additional Lindlar's catalyst (8 mg; Pd/CaCO<sub>3</sub>;  
Aldrich) was then added and stirring was continued under  
an atmosphere of H<sub>2</sub> at 0°C for 25 min, after which  
reaction was complete. The mixture was filtered, and the  
filtrate was concentrated in vacuo. The residue was  
15 purified by preparative HPLC (YMC S5 ODS 20 x 100 mm  
column; flow rate = 20 mL/min; continuous 20 min gradient  
from 80:20 B:A to 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA  
and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Part A compound  
(22 mg; 56%) as a colorless oil.

20

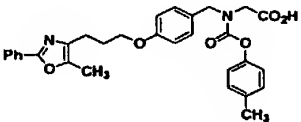
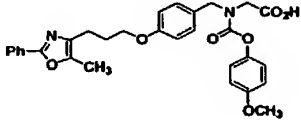
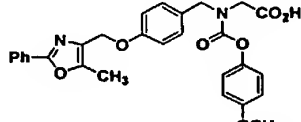
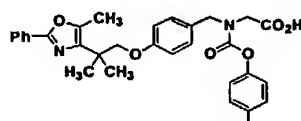
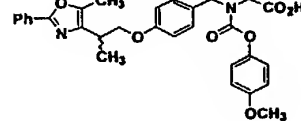
B.



25 To a solution of Part A compound (3 mg; 0.005 mmol)  
in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was added dropwise TFA (0.25 mL) and  
the reaction was stirred for 2 h at RT. Volatiles were  
removed in vacuo; the residue was dissolved in CDCl<sub>3</sub>,

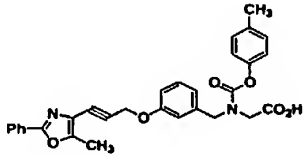
5        Following procedures set out above, Examples 546 to  
556 compounds were prepared.

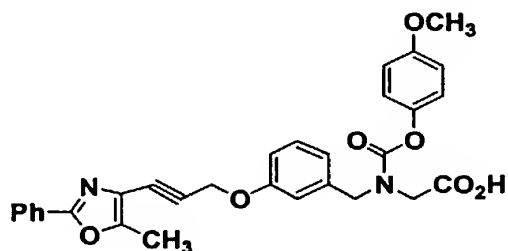
CC1=C(C(=O)O)N(C1Cc2ccc(Oc3ccccc3R1)C(=O)N)Cc4ccc(Oc5c(C)nc(c5)C6=CC=CC=C6)cc4

Example No.	Structure	[M+H] <sup>+</sup>
546		515.4
547		531.3
548		503.3
549		529.4
550		531.2

Cc1c(C(=O)OCCNC(Cc2ccc(OC(=O)c3ccc(R1)cc3)cc2)cc1)nn1ccccc11

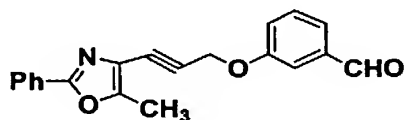
- 281 -

Example No.	Structure	[M+H] <sup>+</sup>
556		511.4

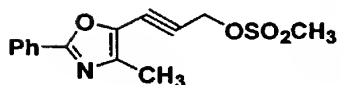
Example 555

5

A.



10 A mixture of the mesylate (124 mg; 0.43 mmol),

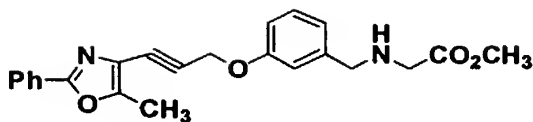


3-hydroxybenzaldehyde (62 mg; 0.51 mmol) and K<sub>2</sub>CO<sub>3</sub> (94 mg; 0.68 mmol) in CH<sub>3</sub>CN (10 mL) were heated at 70°C for 48 h.

15 The reaction was cooled to RT, EtOAc was added, and the mixture was washed with aq 1M NaOH and brine. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; hex:EtOAc 4:1) to give Part A compound (71 mg; 52%) as a colorless

20 oil. [M + H]<sup>+</sup> = 318.2

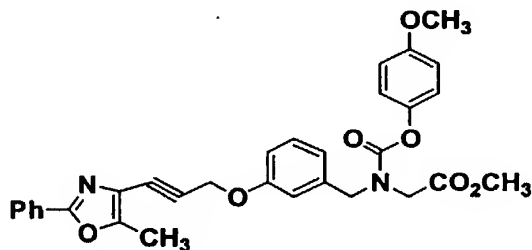
B.



5 To a mixture of Part A compound (71 mg; 0.22 mmol),  
glycine.HCl (140 mg; 1.11 mmol) and Et<sub>3</sub>N (0.3 mL; 2.16  
mmol) in 1,2 dichloroethane (10 mL) was added NaBH(OAc)<sub>3</sub>  
(150 mg). After stirring at RT for 16 h (reaction  
incomplete), more NaBH(OAc)<sub>3</sub> (150 mg) was added. A final  
10 addition of NaBH(OAc)<sub>3</sub> (150 mg; in total 2.12 mmol) was  
made after another 3 h and the reaction stirred for 48 h  
at RT. The reaction was complete at this point;  
saturated aqueous NaHCO<sub>3</sub> was added and the aqueous phase  
was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x). The combined organic  
15 extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and  
concentrated in vacuo. The residue was chromatographed  
(SiO<sub>2</sub>; hex:EtOAc = 4:6) to give Part B compound (81 mg;  
93%) as a colorless oil.

20

C.

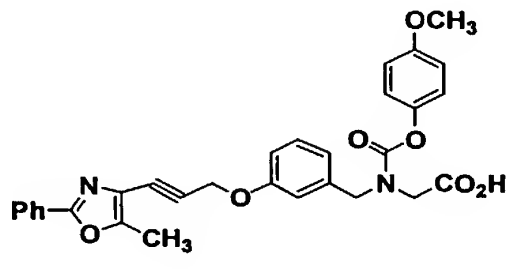


To a solution of Part B compound (10 mg; 0.026  
25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) were successively added pyridine  
(10 μL; 0.12 mmol) and 4-methoxyphenyl chloroformate (10  
μL; 0.067 mmol) (each in 0.1 mL CH<sub>2</sub>Cl<sub>2</sub>). The reaction was  
stirred at RT for 16 h, then partitioned between aqueous  
1N HCl and EtOAc. The organic phase was washed with  
30 brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The  
residue was purified by preparative HPLC (YMC S5 ODS 30 x

75 mm column, flow rate = 20 mL/min; continuous gradient from 70:30 A:B to 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Part C compound (9 mg; 65%).

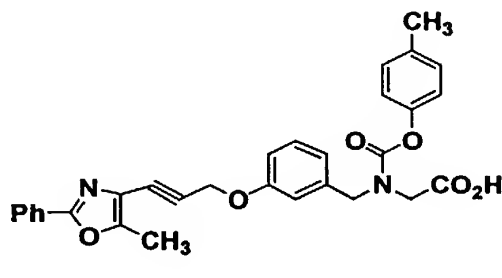
5

D.



10 A solution of Part C compound (9 mg; 0.017 mmol) in 2:1 THF:H<sub>2</sub>O (3 mL) was added LiOH (6 mg; 0.14 mmol). The solution was stirred at RT for 4 h, then acidified with excess 1M HCl (aq). The solution was extracted with EtOAc (2 x 5 mL). The combined organic extracts were  
15 washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The crude product was purified by preparative HPLC using the same conditions as above to give title compound (6 mg; 68%) as a colorless film.  
[M + H]<sup>+</sup> = 527.2

20

Example 556

25

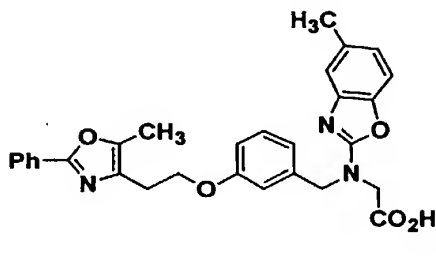
Title compound was synthesized using the same sequence as Example 555 compound from Example 555 Part B compound. Acylation with 4-methyl chloroformate (67% after HPLC purification) followed by LiOH hydrolysis



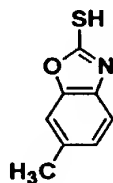
furnished title compound (5 mg; 57% after HPLC purification).  $[M + H]^+ = 511.4$

Example 557

5



A.

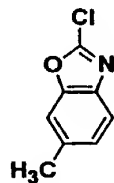


10

A solution of 2-amino-5-cresol (5.0 g; 40 mmol), KOH (3.2 g; 57 mmol) was refluxed in EtOH (50 mL) and CS<sub>2</sub> (40 mL) for 8 h, after which the reaction mixture was concentrated in vacuo. The residue was partitioned between aq 1M HCl (100 mL) and EtOAc (200 mL). The organic phase was washed with water (2 x 100 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to give Part A compound (4.0 g; 60%) as a white powder.

20

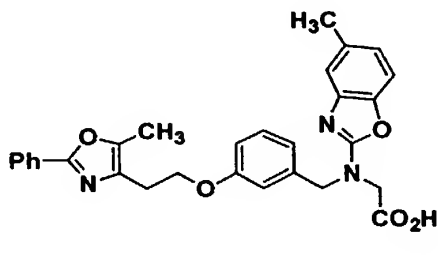
B.



25

A solution of Part A compound (3.2 g; 19 mmol) and POCl<sub>3</sub> (3.75 g; 19 mmol) in toluene (150 mL) was heated at reflux for 2 h. The reaction mixture was washed successively with water and aqueous NaHCO<sub>3</sub>, then dried,

5 c.



20

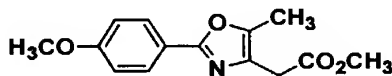
CC1=C(C(=N1)C2=CC=CC=C2)CCOC3=CC=C(C=C3)CN(C3=CC=C(C=C3)N4C(=O)O)Cc5ccc(C)nc5

30

5

COc1ccc(cc1)C2=NC(=C(C)CC2COc3ccc(cc3)CN(C)C(=O)Oc4ccc(OC)cc4)C(=O)OCC(Br)C(=O)CC(=O)OC

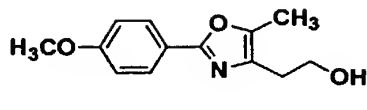
B.



A mixture of Part A compound (1.5 g, 7.2 mmol) and 4-methoxybenzamide (1.0 g, 6.6 mmol) was heated at 100°C for 2.5 h. The reaction mixture was chromatographed

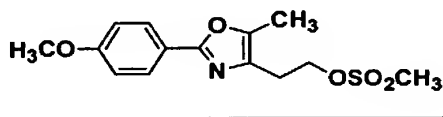
(SiO<sub>2</sub>; 5% acetone/CH<sub>2</sub>Cl<sub>2</sub>) to yield Part B compound (0.57 g, 33%).

C.



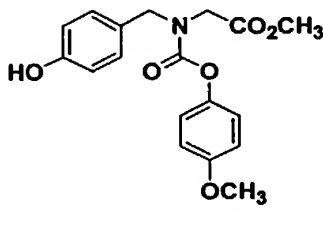
To a solution of the ester (0.57 g, 2.3 mmol) in THF (10 mL) was added  $\text{LiAlH}_4$  (2.5 mL of a 1 M solution in THF, 2.5 mmol) dropwise over 10 min and the reaction was stirred at RT for 0.5 h. The reaction was quenched by adding a few drops of water and then partitioned between EtOAc (50 mL) and brine (10 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to give Part C (0.52 g, >95%) as an oil which was used in the following reaction without further purification.

D.



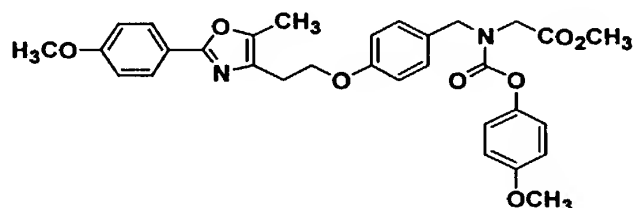
A mixture of Part C compound (0.52 g, 2.3 mmol),  $\text{CH}_3\text{SO}_2\text{Cl}$  (0.25 ml, 3.3 mmol) and  $\text{Et}_3\text{N}$  (0.5 ml, 3.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was stirred at RT for 12 h. Volatiles  
25 were removed in vacuo, and the residue was chromatographed ( $\text{SiO}_2$ ; 4% acetone/ $\text{CH}_2\text{Cl}_2$ ) to provide Part D compound (0.61 g, 85% for 2 steps) as a colorless oil.

**E.**



To a mixture of crude Example 541 Part C compound (synthesized using 4-hydroxybenzaldehyde [2.0 g; 16 mmol] and glycine methyl ester hydrochloride [2.3 g; 18 mmol]) in dioxane:H<sub>2</sub>O (100 mL of a 1:1 mixture) were successively  
5 added NaHCO<sub>3</sub> (2.5 g; 30 mmol; in one portion) and 4-methoxyphenyl chloroformate (2.0 mL; 14 mmol) dropwise. The reaction was stirred at RT for 12 h and then extracted with EtOAc (4 x 150 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo.  
10 The residue was chromatographed (SiO<sub>2</sub>; 3% acetone/CH<sub>2</sub>Cl<sub>2</sub>) to provide Part E compound (2.4 g; 44%) as a colorless oil.

F.

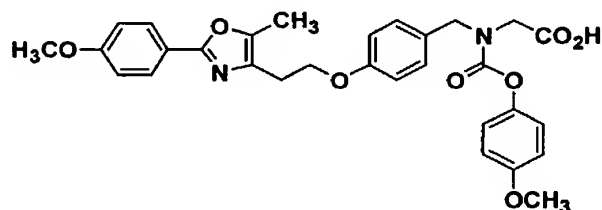


15

A mixture of Part E compound (86 mg, 0.25 mmol), Part D compound (60 mg, 0.20 mmol) and K<sub>2</sub>CO<sub>3</sub> (50 mg, 3.7  
20 mmol) in DMF (3 mL) was heated at 80°C for 12 h. The reaction was cooled to RT and filtered. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; 7:3 hexane:EtOAc) to provide title compound (41 mg; 36%) as a colorless oil.

25

G.

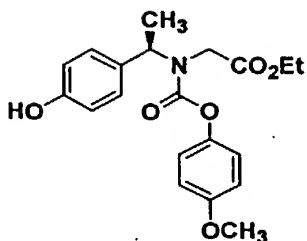


10

## 15

COC(=O)OCC#CC1=C(C)C(=N1)c2ccccc2

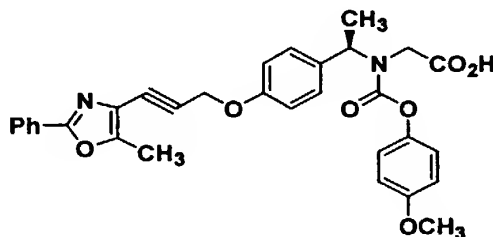
25



[described in the synthesis of Example 503 Part B compound (50 mg; 0.13 mmol)],  $K_2CO_3$  (17 mg; 0.34 mmol) in  $CH_3CN$  (1 mL) were heated at 70°C for 24 h. Additional  
5  $K_2CO_3$  (30 mg) and  $CH_3CN$  (1 mL) were added and the mixture was heated at 75°C for another 48 h. The reaction was cooled to RT, EtOAc was added, and the mixture was washed with aq 1M NaOH and brine. The organic phase was dried ( $Na_2SO_4$ ) and concentrated in vacuo to give the crude  
10 product. This was purified by preparative HPLC (YMC S5 ODS 50 x 75 mm column; continuous gradient from 70:30 B:A to 100% B, where A = 90:10:0.1  $H_2O$ :MeOH:TFA and B = 90:10:0.1 MeOH: $H_2O$ :TFA) to give Part A compound (13 mg; 35%) as a colorless oil.

15

B.



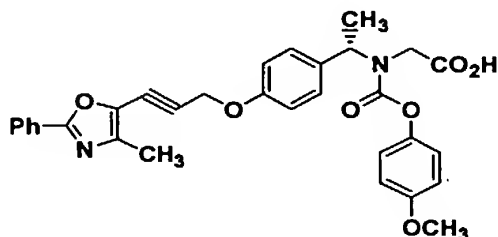
20 To a solution of Part A compound (12 mg; 0.021 mmol) in 2:1 THF: $H_2O$  (1.5 mL) was added LiOH (8 mg; 0.19 mmol). The solution was stirred at RT for 24 h, then acidified with excess 1M HCl (aq). The solution was  
25 extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine, dried ( $Na_2SO_4$ ), and concentrated in vacuo. The crude product was purified by

preparative HPLC using the same conditions as above to give title compound (6.4 mg) as a colorless film.

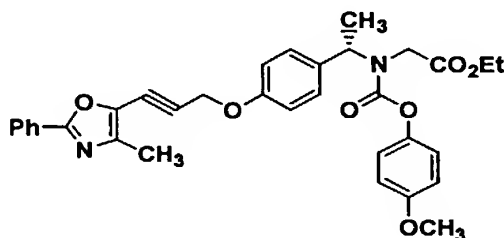
$[M + H]^+ = 541.3$

5

### Example 561



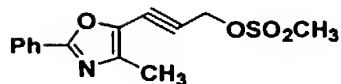
A.



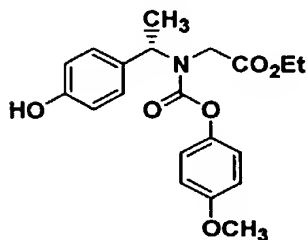
10

A mixture of the mesylate (18 mg; 0.061 mmol)

15



the phenol (50 mg; 0.13 mmol)



20

$K_2CO_3$  (17 mg; 0.34 mmol) in  $CH_3CN$  (1 mL) were heated at  $70^\circ C$  for 24 h. Additional  $K_2CO_3$  (30 mg) and  $CH_3CN$  (1 mL) were added and the mixture was heated at  $75^\circ C$  for another 48 h. The reaction was cooled to RT, EtOAc was added, and the mixture was washed with aq 1M NaOH and brine.



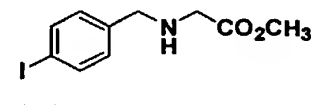
5

Cc1c(C#CCOCC2=CC=C(C=C2)C[C@H](C)N(C(=O)O)C(=O)Oc3ccc(OC)cc3)c4ccccc4n1

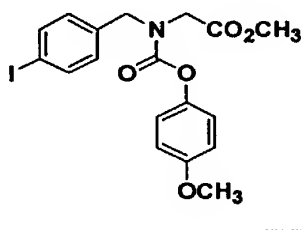
To a solution of Part A compound (12 mg; 0.021 mmol) in 2:1 THF:H<sub>2</sub>O (1.5 mL) was added LiOH (8 mg; 0.19 mmol). The solution was stirred at RT for 24 h, then acidified with excess 1M HCl (aq). The solution was extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The crude product was purified by preparative HPLC using the same conditions as above to give title compound. [M + H]<sup>+</sup> = 541.3

CC1=C(C#CC2=CC=CC=C2CN(C)C(=O)OC3=CC=C(C=C3)OC)C(=Nc4ccccc4)O1C(=O)O

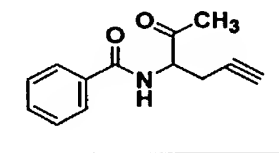
A.



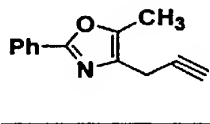
15 B.



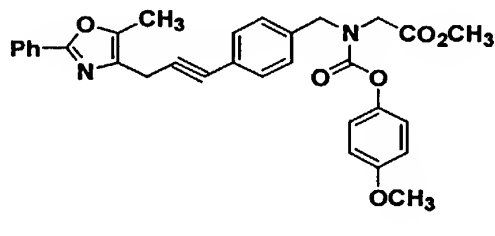
30 C.



15 D.



30 E.



10

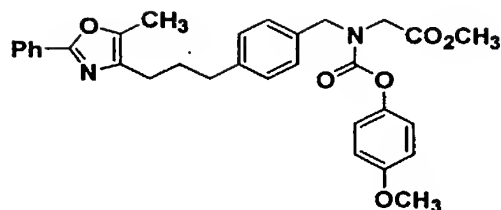
Cc1c(C#CCc2ccc(cc2)CNC(=O)Oc3ccc(OC)cc3)nc(C4=CC=CC=C4)o1

\_\_\_\_\_

25

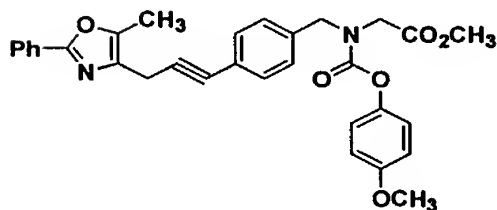
COc1ccc(cc1)OC(=O)N(Cc2ccc(cc2)CCCCc3c(C)c(O)c(c3)c4ccccc4)C(=O)O

A.



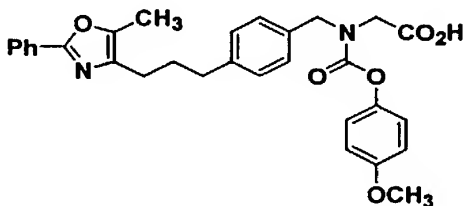
5

A solution of Example 562 Part E compound



(38 mg; 0.072 mmol) in MeOH (5 mL) was stirred under an atmosphere of H<sub>2</sub> in the presence of 10% Pd/C catalyst (10 mg) at RT for 2 h. The catalyst was filtered off and the filtrate was concentrated in vacuo to give Part A compound (35 mg; 92%) as an oil.

B.



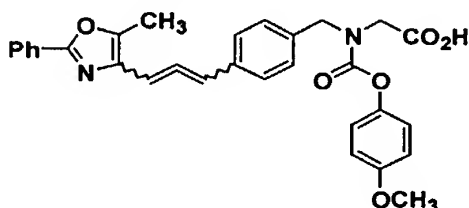
15

A solution of Part A compound (35 mg; 0.066 mmol) in aqueous LiOH (1 mL of a 1M solution) and THF (5 mL) was stirred at RT for 2h. The reaction was acidified to pH 3 with excess aqueous 1M HCl and extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS reverse phase column; 30 x 250 mm; flow rate = 25 mL/min; 30 min continuous gradient from 50:50 A:B to 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B =

90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give, after lyophilization from dioxane, the title compound (31 mg; 87%) as a white solid.  $[M + H]^+ = 515.9$

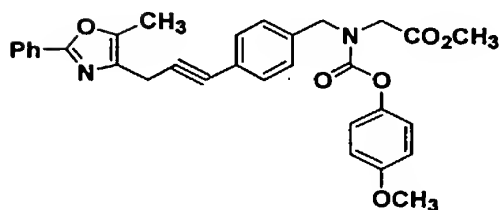
5

### Example 564



10

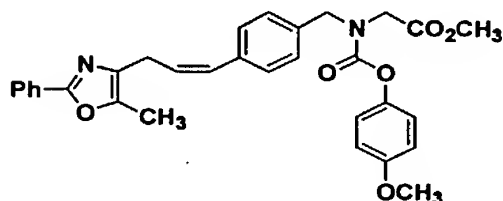
A solution of Example 562 Part E compound



(20 mg; 0.038 mmol) and aqueous LiOH (1 mL of a 1 M solution; 1 mmol) in THF (2 mL) was stirred at RT for 2 h. The reaction mixture was acidified with excess aqueous 1 M HCl and extracted with EtOAc. The combined organic extracts were concentrated in vacuo. The residue was purified by preparative HPLC ((YMC S5 ODS reverse phase column; 30 x 250 mm; flow rate = 25 mL/min; 30 min continuous gradient from 50:50 A:B to 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give (9 mg; 46%) as a white solid. [M + H]<sup>+</sup> = 511.2

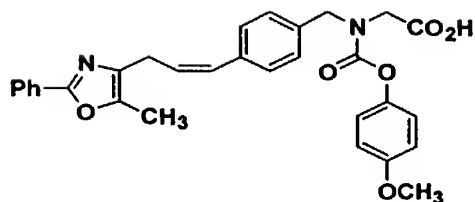
Cc1c(C=Cc2ccc(cc2)CN(Cc3ccc(cc3)OC(=O)O)C(=O)Oc4ccc(OC)cc4)nc5ccccc5o1

A.

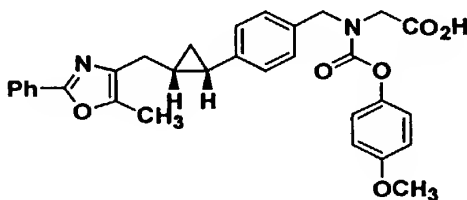
CCOC1=CC=C(OC(=O)NCCc2ccc(cc2)/C=C/Cc3nc(C)c(oc3-c4ccccc4)C1

- 299 -

B.

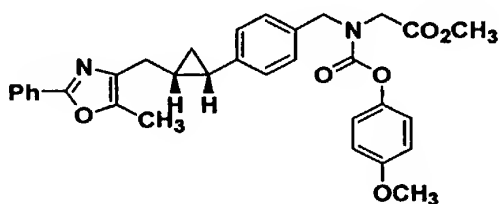


- A solution of Part A compound and aqueous LiOH (1 mL  
5 of a 1 M solution; 1 mmol) in THF was stirred at RT  
overnight. The reaction mixture was acidified with  
excess aqueous 1 M HCl and extracted with EtOAc (2x).  
The combined organic extracts were concentrated in vacuo.  
The residue was purified by preparative HPLC (as for  
10 Example 495) to give the title compound (14 mg; 18%) as a  
white solid.  $[M + H]^+ = 513.3$

Example 566 (racemic)

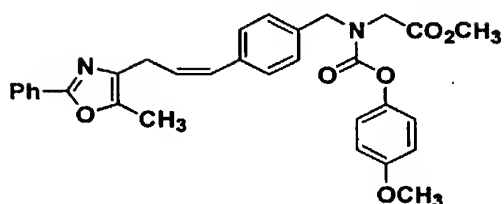
15

A.





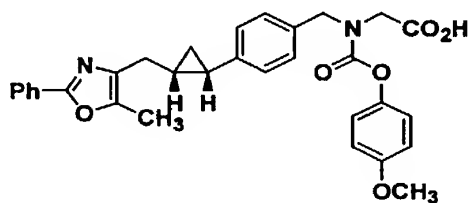
To a 0°C solution of Example 565 Part A compound



(60 mg; 0.11 mmol) in DCE (3 mL) was added dropwise diethylzinc (43  $\mu$ L; 0.29 mmol). The solution was stirred at 0°C for 10 min and iodochloromethane (244  $\mu$ L; 0.57 mmol) was then added. The reaction was allowed to warm to RT and stirred at RT for 3 h, then was cautiously quenched by addition of aqueous HCl (1 mL of a 1 M solution). The aqueous layer was extracted with EtOAc (2x); the combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; stepwise gradient from 3:1 to 2:1 hexane:EtOAc) to give crude Part A compound, which was used in the next step without further purification.

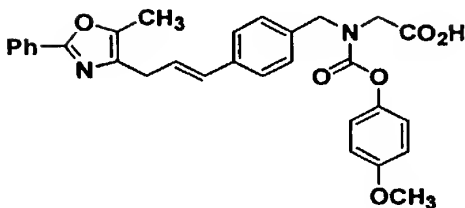
15

B.



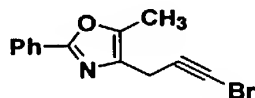
A solution of crude Part A compound and aqueous  
20 LiOH (1 mL of a 1 M solution; 1 mmol) in THF was stirred  
at RT overnight. The reaction mixture was acidified with  
excess aqueous 1 M HCl and extracted with EtOAc. The  
combined organic extracts were concentrated in vacuo.  
The residue was purified by preparative HPLC (conditions)  
25 to give the title compound (7 mg; 12% over 2 steps) as a  
white solid.  $[M + H]^+ = 527.2$ .

### Example 567



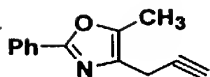
5

A.



A mixture of Example 562 Part D compound

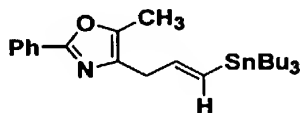
10



15

(300 mg; 1.52 mmol), N-bromo-succinimide (297 mg; 1.67 mmol) and AgNO<sub>3</sub> (28 mg; 0.19 mmol) in acetone (2 mL) was stirred at RT for 30 min. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; hexane:EtOAc 5:1) to give Part A compound (320 mg; 76%) as yellow crystals.

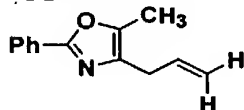
B.



20

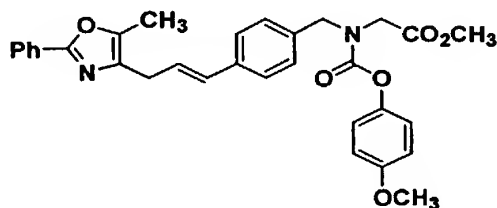
To a solution of Part A compound (320 mg; 1.2 mmol),  $\text{Ph}_3\text{P}$  (13 mg; 0.05 mmol) and  $\text{Tris}(\text{dibenzylidene-acetone})\text{dipalladium}(0)$  (5 mg; 0.006 mmol) in THF (1 mL) was added  $\text{Bu}_3\text{SnH}$  (700  $\mu\text{L}$ ; 2.5 mmol) dropwise under an atmosphere of  $\text{N}_2$ . The mixture was stirred at RT for 2 h, then was quenched by addition of aqueous KF (7 mL of a 1 M solution). The mixture was stirred vigorously overnight, then extracted with EtOAc (2x). The combined organic extracts were washed with  $\text{H}_2\text{O}$ , dried ( $\text{Na}_2\text{SO}_4$ ) and

concentrated in vacuo. The residual oil was chromatographed (SiO<sub>2</sub>; hexane:EtOAc 3:1) to give Part B compound (200 mg; 35%) as an oil. In addition, the byproduct vinyl compound

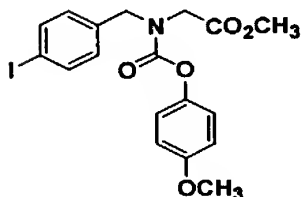


(100 mg; 43%) was also obtained.

C.

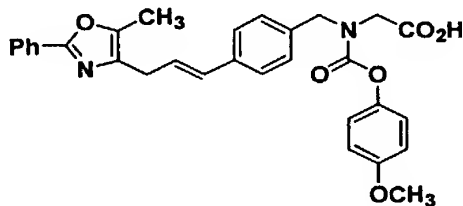


A solution of Part B compound (100 mg; 0.020 mmol) and Example 562 Part B compound



(100 mg; 0.22 mmol) and (Ph<sub>3</sub>P)<sub>4</sub>Pd<sup>0</sup> (3 mg; 0.002 mmol) in toluene was heated at 100°C overnight under an atmosphere of N<sub>2</sub>. Volatiles were removed in vacuo and the residue was chromatographed (SiO<sub>2</sub>; stepwise gradient from 3:1 to 2:1 hexane:EtOAc) to give Part C compound.

D.

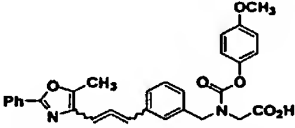
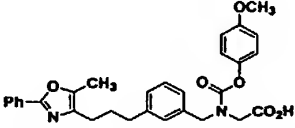
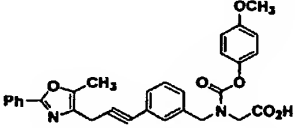
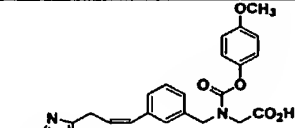
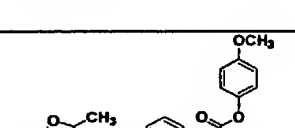


A solution of crude Part C compound (in aqueous LiOH (1 mL of a 1M solution) and THF (5 mL) was stirred

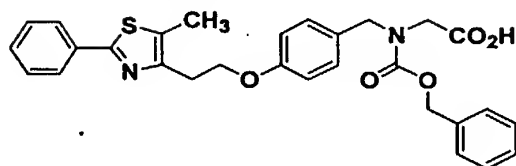
at RT overnight. The reaction was acidified to pH 3 with excess aqueous 1 M HCl and extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC S5 ODS reverse phase column; 30 x 250 mm; flow rate = 25 mL/min; 30 min continuous gradient from 50:50 A:B to 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give, after lyophilization from dioxane, title compound (23 mg; 20%) as a white solid. [M + H]<sup>+</sup> = 513.3

### Examples 568 to 572

Following the procedures set out hereinbefore and in the working Examples, the following compounds were prepared.

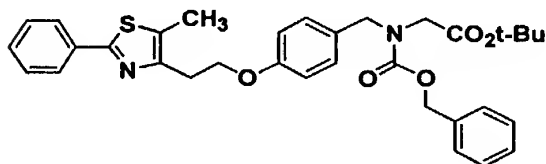
Example No.	Structure	[M+H] <sup>+</sup>
568		511.2
569		515.9
570		511.2
571		513.2
572		513.3

### Example 573

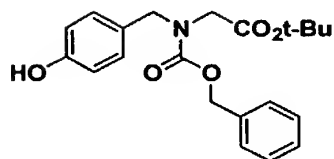


5

A.

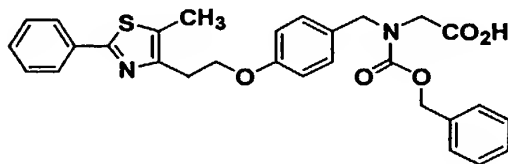


10 To a mixture of the amino-ester (27 mg; 0.073 mmol)



5-methyl-2-phenyl-thiazol-4-yl-ethanol (25 mg; 0.11 mmol; Maybridge) resin-bound  $\text{Ph}_3\text{P}$  (27 mg; 0.081 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was added DEAD (20  $\mu\text{L}$ ; 0.13 mmol). The reaction was stirred at RT for 6 h, then was filtered. The filtrate was concentrated in vacuo and the residue was purified by preparative HPLC (YMC S5 ODS 30 x 100 mm column; flow rate = 50 mL/min; continuous gradient from 30:70 B:A to 100% B, where solvent A = 90:10:0.1  $\text{H}_2\text{O}$ :MeOH:TFA and solvent B = 90:10:0.1 MeOH: $\text{H}_2\text{O}$ :TFA) to furnish Part A compound.

B.

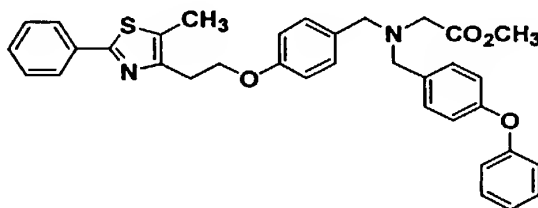


25

5

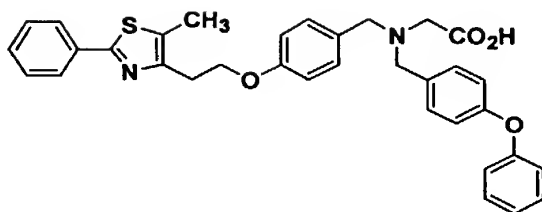
CC1=C(CCOc2ccc(cc2)CN(Cc3ccc(cc3)Oc4ccccc4)C(=O)O)N=C(N1)c5ccccc5

A.

CCOC(=O)N(Cc1ccc(O)cc1)Cc2ccc(Oc3ccccc3)cc2

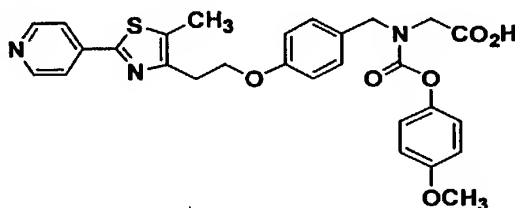
5-methyl-2-phenyl-thiazol-4-yl-ethanol (25 mg; 0.11 mmol; Maybridge) resin-bound  $\text{Ph}_3\text{P}$  (32 mg; 0.096 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was added DEAD (20  $\mu\text{L}$ ; 0.13 mmol). The reaction was stirred at RT for 6 h, then was filtered. The filtrate was concentrated in vacuo to give crude Part A compound.

B.

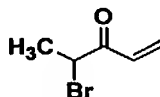


5 A solution of crude Part A compound and LiOH.H<sub>2</sub>O (20 mg; 0.48 mmol) in THF:MeOH:H<sub>2</sub>O (1 mL of a 3:1:1 mixture) was stirred at RT overnight. The reaction was acidified to pH ~4 with aqueous 1N HCl, then was extracted with EtOAc (2x). The combined organic extracts  
10 were concentrated in vacuo and the residue was purified by preparative HPLC (YMC S5 ODS 30 x 100 mm column; flow rate = 50 mL/min; 10 min continuous gradient from 30:70 B:A to 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to furnish title  
15 compound (16 mg; 34%) as a brown oil (95% purity by analytical HPLC). [M + H]<sup>+</sup> = 565.2

### Example 575



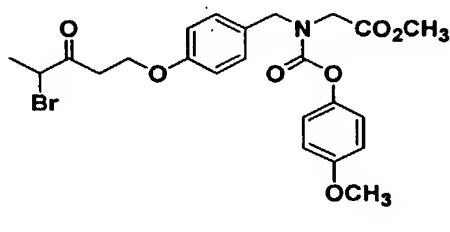
A.



25 To a solution of 2,4-dibromo-3-pentanone (Avocado Chemicals, 19.6 g, 80 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added dropwise  $\text{Et}_3\text{N}$  (30 mL, 210 mmol) over 30 min; the resulting solution was heated to reflux for 12 h. The reaction mixture was cooled to RT, then was poured into ice and

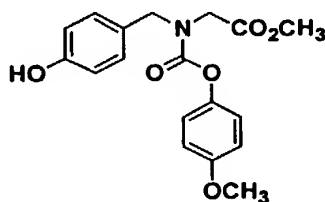
acidified with concentrated HCl. The organic phase was concentrated in vacuo to give an oil, which was fractionally distilled (b.p. = 42°-45°C at 13 mm Hg) to give Part A compound (6.0 g, 46%; with ~20% of the starting material) as an oil.

B.



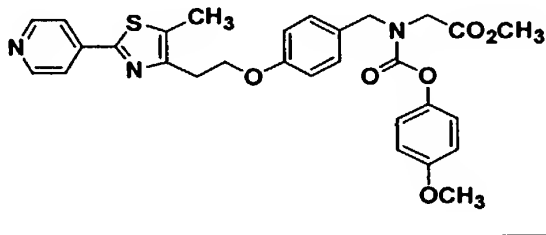
10

A mixture of Example 559 Part E compound (0.60 g, 1.7 mmol),



Part A compound (0.60 g, 3.7 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.0 g, 7.3 mmol) in benzene (20 mL) was stirred at RT for 12 h. TLC at this point indicated that ~50% of the starting material had been consumed and that the reaction had stalled. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed (SiO<sub>2</sub>; 3% acetone/CH<sub>2</sub>Cl<sub>2</sub>) to provide Part B compound (0.41 g; 47%) as an oil.

C.

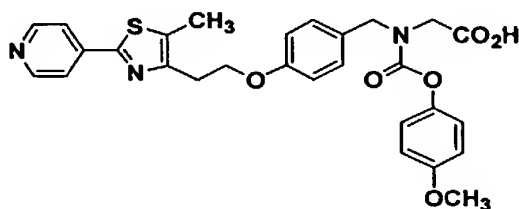


25



A solution of Part B compound (40 mg, 0.080 mmol) and thioisonicotinamide (50 mg, 0.36 mmol) in toluene-EtOH (3 mL of a 1:1 mixture) was heated at 55°C for 12 h. The reaction was cooled to RT and volatiles were removed in vacuo. The crude product was purified by preparative HPLC (YMC S5 ODS 30 x 250 mm, continuous 30 min gradient from 30% B:70% A to 100% B at 30 min, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA) to give Part C compound (17; 39%) as an oil.

D.



A solution of Part C compound (17 mg, 0.031 mmol) and LiOH.H<sub>2</sub>O (40 mg, 1 mmol) in THF-H<sub>2</sub>O (3 mL of a 2:1 mixture) was stirred at RT for 2 h. The reaction mixture was acidified by addition of acetic acid and then partitioned between H<sub>2</sub>O (2 mL) and EtOAc (5 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo to provide the title compound (13.7 mg, 81%) as a white solid. [M + H]<sup>+</sup> = 534.2



5

· 10

· 10

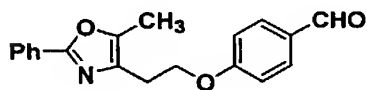
- 311 -

COC1=CC=C(SC(=O)N(CCC2=C(C)C(=O)N2C3=CC=CC=C3)CC4=CC=C(OC)C=C4)C=C1

10

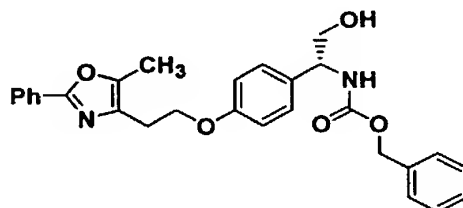
CCCC[C@H](Cc1ccc(OCC2=C(C)N(C2)c3ccccc3)cc1)C(=O)NCC(=O)Oc4ccc(OC)cc4C(=O)OCC1=CC=C(C=C1)OCCc2c(C)c(Oc3ccccc3)n2

To a -78°C solution of methyltriphenylphosphonium bromide (4.2 g; 11.8 mmol) in THF (60 mL) was added dropwise n-butyllithium (4.7 mL of a 2.5 M solution in hexane; 11.8 mmol). The solution was allowed to warm to RT and stirred at RT for 45 min. To this mixture was added dropwise a solution of the aldehyde (3.0 g; 9.8 mmol)



5

10



15

20

25

30

CC1=C(C2=CC=CC=C2N=C2C(=C1)C=C2C3=CC=CC=C3)CCOC4=CC=C(C=C4)C[C@H](C5=CC=CC=C5)C(=O)OCC6=CC=CC=C6

5

To a 0°C solution of Part B compound (1.10 g; 2.33 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) were successively added methanesulfonyl chloride (220 µL; 2.80 mmol) and Et<sub>3</sub>N (420 µL; 3.03 mmol) dropwise. The reaction was stirred at 0°C for 2 h, then was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and aqueous 1N HCl. The organic phase was washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to provide Part D compound (1.10 g; 86%) as a solid.

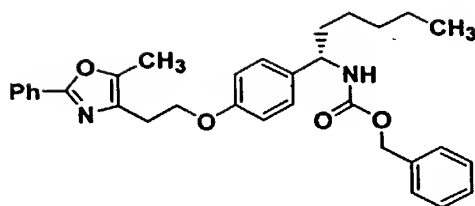
15

CC1=C(C2=CC=CC=C2N=C3C(=C1)OC(=C3)C4=CC=CC=C4)CCOC5=CC=C(C=C5)C[C@H](C6=CC=CC=C6)C(=O)NC7=CC=CC=C7Br

A mixture of Part D compound (1.10 g; 2.0 mmol) and  
20 LiBr (260 mg; 3.0 mmol) in acetone (4 mL) was heated at  
50°C for 14 h. The reaction was then cooled to RT and  
concentrated in vacuo. The residue was chromatographed  
(SiO<sub>2</sub>; stepwise gradient from 9:1 to 4:1 hex:EtOAc) to  
give Part E compound (481 mg; 45%) as an oil.

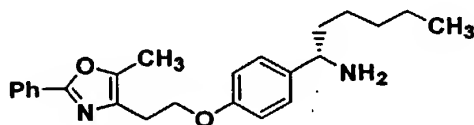
25

**F.**



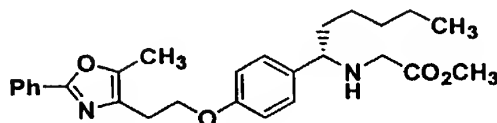
To a  $-78^{\circ}\text{C}$  slurry of  $\text{CuCN}$  (17 mg; 0.19 mmol) in freshly distilled anhydrous THF (0.54 mL) was added dropwise *n*-butyllithium (150  $\mu\text{L}$  of a 2.5 M solution in hexanes). The mixture was allowed to warm slowly to  $0^{\circ}\text{C}$  to generate the higher-order cuprate reagent as a clear tan solution. The reaction was then cooled to  $-50^{\circ}\text{C}$  and a solution of Part E compound (50 mg; 0.094 mmol) in THF (0.4 mL) was added dropwise. The reaction was stirred at  $-50^{\circ}\text{C}$  for 1h and then allowed to warm slowly to  $0^{\circ}\text{C}$  over 2h. The mixture was then quenched at  $0^{\circ}\text{C}$  by addition of 9:1 saturated aqueous  $\text{NH}_4\text{Cl}$ :concentrated  $\text{NH}_4\text{OH}$  (2 mL), and then allowed to warm to RT with vigorous stirring until complete dissolution had occurred. The aqueous phase was extracted with EtOAc (2x), and the combined organic extracts were washed with saturated aqueous  $\text{NH}_4\text{Cl}$  and brine, dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. The residue was chromatographed ( $\text{SiO}_2$ ; stepwise gradient from 9:1 to 2:1 hex:EtOAc) to provide Part F compound (26 mg; 54%) as a solid.

G.



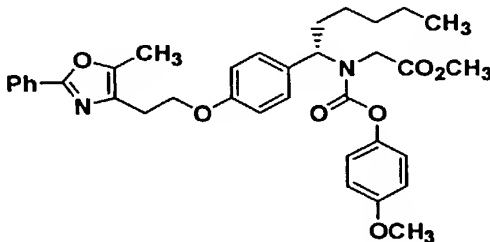
A mixture of Part F compound (26 mg; 0.051 mmol) and 10% palladium on carbon (10 mg) in 2:1 MeOH:EtOAc (1.2 mL) was stirred under an atmosphere of H<sub>2</sub> (balloon) at RT for 2 h, at which point the reaction was complete by HPLC. The catalyst was filtered off through Celite®

H.



10 The reaction mixture was partitioned between H<sub>2</sub>O and EtOAc (60 mL) each. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to furnish crude Part H compound, which was used in the next step without further purification.

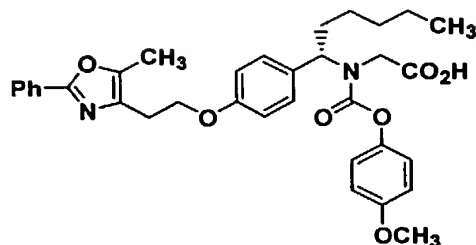
I.



- 316 -



J.

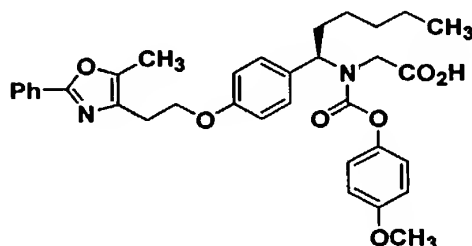


To a solution of Part I compound (9.0 mg; 0.015 mmol) in THF:H<sub>2</sub>O (750 µL of a 2:1 solution) was added LiOH.H<sub>2</sub>O (2.5 mg; 0.06 mmol). The reaction was stirred at RT for 15 h; then EtOAc (2 mL) was added and the solution acidified with 1 N HCl solution to pH ~ 2. The organic phase was washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by preparative HPLC (YMC reverse phase ODS 20 x 100 mm column; flow rate = 20 mL/min; 10 min continuous gradient from 50:50 B:A to 100% B + 10 min hold-time at 100% B, where solvent A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA and solvent B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA; retention time = 13.2 min) to provide the title compound (6.0 mg; 68%) as a white solid.

$$[M + H]^+ = 587.3$$

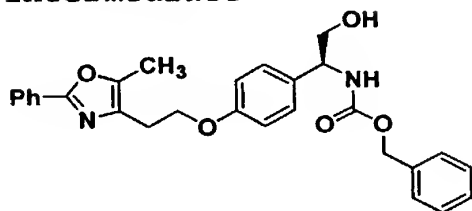
### Example 586

25



The synthesis of Example 586 was performed using the identical sequence as described for Example 585 except

that the catalyst used in the aminohydroxylation procedure (step 2) for the preparation of the key intermediate

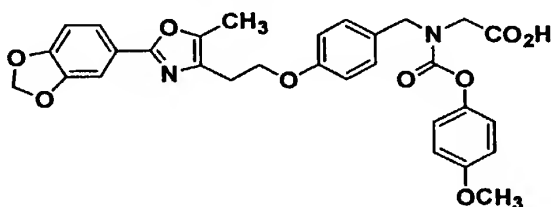


5

was hydroquinine 1,4-phthlazinediyl diether [(DHQ)<sub>2</sub>PHAL; Aldrich] instead of hydroquinidine 1,4-phthlazinediyl diether [(DHQD)<sub>2</sub>PHAL; Aldrich].

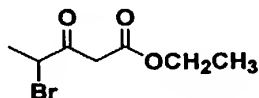
10

Example 587



15

A.

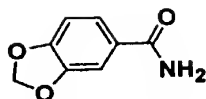


20

25

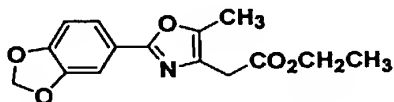
To a 0°C solution of ethyl propionylacetate (10.0 g, 69.4 mmol) in CHCl<sub>3</sub> (60 mL) was added dropwise a solution of Br<sub>2</sub> (3.6 mL; 69.4 mmol) in CHCl<sub>3</sub> (20 mL) and the resulting mixture was stirred at 0°C for 0.5 h. The reaction was allowed to warm to RT and stirred at RT for 0.5 h. Air was then bubbled into the mixture for 1 h. Volatiles were then removed in vacuo to yield an oily residue to provide crude Part A compound (15.3 g, >95% yield) as an oil which was used in the next reaction without further purification.

B.



To a mixture of piperonylic acid (2.0 g; 12 mmol), HOBT.H<sub>2</sub>O (2.44 g; 18.1 mmol) and NH<sub>4</sub>Cl (1.28 g; 23.7 mmol) in DMF (48 mL) were successively added EDCI.HCl (3.45 g; 18.1 mmol) and iPr<sub>2</sub>NEt (2.3 mL; 48 mmol). The reaction mixture was stirred at RT overnight until the starting acid had been completely consumed (by HPLC). The mixture was partitioned between H<sub>2</sub>O (80 mL) and EtOAc (250 mL). The aqueous phase was extracted with EtOAc (250 mL). The combined organic extracts were washed with aqueous 1 N HCl (40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The crude product was chromatographed (SiO<sub>2</sub>; stepwise gradient from hex:EtOAc 1:1 to 100% EtOAc) to give Part B compound (1.5 g; 76 %) as a white solid.

C.

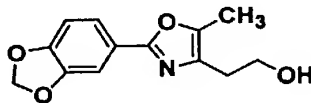


20

A mixture of Part A compound (2.11 g, 9.5 mmol) and Part B compound (1.41 g, 8.54 mmol) was heated with a heat gun until the mixture became homogeneous, after which the solution was heated at 130°C in an oil bath for 5 h. The reaction mixture was chromatographed (SiO<sub>2</sub>; continuous gradient from hex to 4:1 Hex:EtOAc over 20 min, then continuous gradient from 4:1 Hex:EtOAc to 100% EtOAc over 15 min) to yield Part C compound (0.95 g, 39%) as a yellow solid.

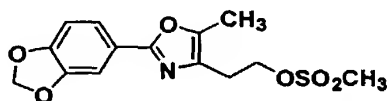
30

D.



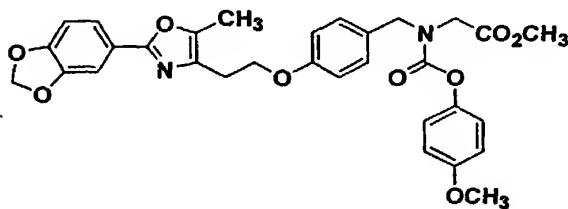
10

15

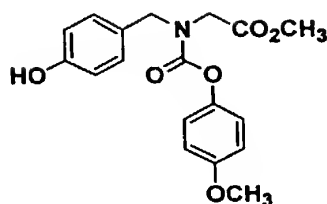


20

**F.**

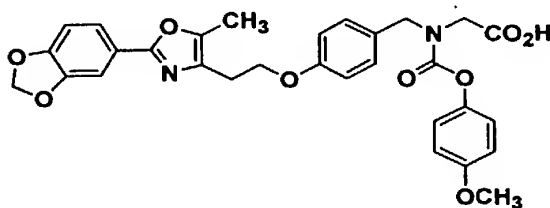


30



and K<sub>2</sub>CO<sub>3</sub> (15 mg, 0.109 mmol) in acetonitrile (1 mL) was shaken and heated at 80°C for 22 h. The reaction was cooled to RT and filtered. The filtrate was concentrated in vacuo and the residue was purified by preparative HPLC (YMC reverse-phase ODS 20 x 100 mm column; continuous gradient over 10 min from 70:30 A:B to 100% B, where A = 90:10:0.1 H<sub>2</sub>O:MeOH:TFA, and B = 90:10:0.1 MeOH:H<sub>2</sub>O:TFA, with 7 min hold time at 100% B; flow rate = 20 mL/min) to provide Part F compound (21 mg; 51%) as a colorless oil.

G.



15

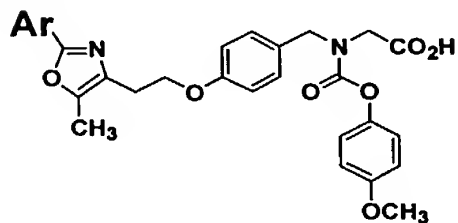
A solution of Part F compound (21 mg, 0.037 mmol) and LiOH·H<sub>2</sub>O (4.0 mg; 0.095 mmol) in THF-H<sub>2</sub>O (2.0 mL of a 1:1 mixture) was shaken at RT for 4 h. The reaction mixture was acidified to pH 5 with 1 M aqueous HCl, then was extracted with EtOAc (3 mL) by shaking for 10 min. The organic phase was washed with H<sub>2</sub>O (2 mL) and concentrated in vacuo to provide Example 586 (16.3 mg, 75%) as a solid foam.

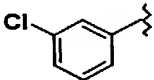
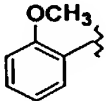
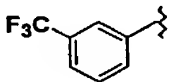
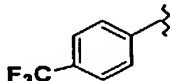
$$[M + H]^+ = 561.2$$

25

Examples 588 to 596 were prepared according to the scheme described above.

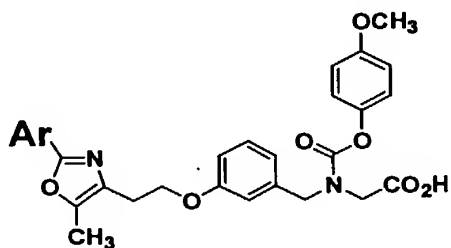
Examples 588 to 591



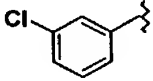
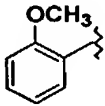
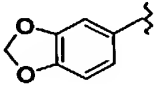
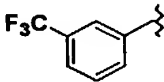
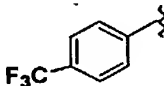
Example No.	Ar	[M+H] <sup>+</sup>
588		551.1
589		547.2
590		585.3
591		585.2

5

Examples 592 to 596



10

Example No.	Ar	[M+H] <sup>+</sup>
592		551.1
593		547.2
594		561.2
595		585.3
596		585.2